Abstract Book

Nordic Conference on Future Health

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Jonna Pauliina Clancy[1], MD Janina Forstén[1], BS Elina Koskinen[1], Adj. prof Satu Koskela[1], Adj. prof Mikko Arvas[1], Phd Kimmo Pitkänen[1]
[1]Finnish Red Cross Blood Service

75: Genome-wide association study reveals the unique genetic structure of active blood donors
Jonna Pauliina Clancy[1], Phd Jarkko Toivonen[1], MD Jouni Lauronen[1], Adj.prof Satu Koskela[1], Prof Jukka Partanen[1], FinnGen FinnGen[2], Adj.prof Mikko Arvas[1], Phd Jarmo Ritari[1]
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76: Exploring the impact of exclusion criteria on the genetic architecture of Major Depressive Disorder in Danish biobanks
Mischa Lundberg[1], Morten Krebs[1], Christian Erikstrup[2], Ole B. Pedersen[3], Erik Sørensen[4], Hreinn Stefansson[5], Thomas Werge[1], Sisse R. Ostrowsk[4], Andrew J. Schork[1]
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Genomics and Proteomics of Heart Disease Risk Prediction in the Trøndelag Health Study
Karianne Skjærstein[1], Ida Surakka[2], Therese Haughdal Nøst[1,3], Prof Kristian Hveem[1,4], Brooke Wolford[1]
[1]Center for Molecular and Clinical Epidemiology, Department of Public Health and Nursing, Norwegian University of Science and Technology, [2]Department of Internal Medicine: Cardiology, University of Michigan, [3]Department of Community Medicine, UiT The Arctic University of Norway,

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Evaluating the Predictive Ability of Polygenic Risk Scores for Intrahepatic Cholestasis of Pregnancy in the Estonian Biobank
Fanny-Dhelia Pajuste[1], Kristi Läll[1], Triin Laisk[1], Prof Reedik Mägi[1]
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80: A plasma protein-based risk score to predict hip fractures
Eivind Coward[1], Thomas R. Austin[2], Maria Nethander[3,4], Howard A. Fink[5,6], Anna E. Törnqvist[3], Diana I. Jalal[10,11], Joshua I. Barzilay[12], Kristian Hveem[1,7,8], Claes Ohlsson[3,9]
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81: Biobanking and sample processing in the IMPRESS-Norway study
Britina Kjuul Danielsen[1], Tonje Dalen[1]
[1]Oslo University Hospital

82: Large-scale protein-disease risk association analysis in the UK Biobank: Introducing an extensive and freely available research resource in Olink® Insight
PhD Ola Caster[1], PhD Linn Fagerberg[1], Hilda Andersson, PhD Markus Sällman Almén[1], PhD Ida Grundberg[1]
[1]Olink Proteomics

84: Engagement with children from marginalised communities in India regarding gene research and tailored treatments for children's asthma and allergy. pos
Rajlakshmi Sohini Mukhopadhyay[1], Dr Ciara Holden[2], Ms Olivia Cottington[1], Prof Somnath Mukhopadhyay[2]
[1]University Hospitals Sussex Foundation Trust, [2]Brighton and Sussex Medical School

85: Genome-wide association analysis of infertility in men and women
Astanand Jugessur[1], Yunsung Lee, Ben Brumpton, Maria Christine Magnus
[1]Norwegian Institute Of Public Health/university Of Bergen

86: Optimized Library Preparation Kit and Workflow for Improving cfDNA Sequencing Sensitivity
Christofer Flood[1]
[1]Twist Bioscience

87: Towards elimination of cervical cancer – increased use of biobanks enables rapid assessment of emerging biomarkers in screening
Eva Wessel Stratford[1], Kristin Knoll[2], Kristina Wunsch[2], Thea E Hetland Falkenthal[1], Ståle Nygård[1], Mari Nygård[1]
[1]Cancer Registry of Norway, Norwegian Institute of Public Health, [2]Oncgnostics GmbH

89: Circulating RNAs prior to endometrial cancer diagnosis

Sina Rostami[1,2], Prof Trine B Rounge[1,3], Dr. Luca Pestarino[1,4], Dr. Robert Lyle[5,6], Dr. Renée T. Fortner[1,7], Prof Øystein Ariansen Haaland[8], Prof Rolv T. Lie[6,8], Prof Fredrik Wiklund[9], Prof Tone Bjørge[8,10], Dr. Hilde Langseth[1,11]
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90: Enriching the hospital biobank collections with diagnostic leftover samples and returned data
Merja Perälä[1], Roosa E Kallionpää, Niina Pitkänen, Satu Koskinen, Perttu Terho, Lila Kallio
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91: Chemokine CCL23 as a diagnostic and prognostic biomarker in systemic Mastocytosis
MSc Kajsa Ax[1], MD, PhD Cecilia Karlström[1], MD Elin Ljung[1], MD, PhD Stina Söderlund[2], MSc Daryl Boey[3], PhD Hong Qian[1], PhD Joakim Dahlin[3], MD, PhD, Professor Johanna Ungerstedt[4]
[1]Department of Medicine, Karolinska Institutet, [2]Akademiska Hospital, [3]Department of Medicine, Karolinska Institutet, [4]Department of BKV, Linköping University

92: KI Biobank - A Research-Integrated Biobank
PhD Li-Sophie Rathje[1], BMA Ann-Christin Carman[1], Camilla Lagerberg[1], PhD Michiko Mori[1], Nasrin Bavand[1], MLM Nasrin Bavand[1], PhD Virpi Björkman[1], PhD Sanela Kjellqvist[1]
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94: The Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research, a longitudinal cohort biobank – A gold mine for population-based research.pos
PhD Marina Mola Caminal, PhD Anna-Karin Kolseth, Prof, PhD Karl Michaëlsson
[1]SIMPLER Biobank, Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University

95: Automated vs. Manual Ultra-Low Temperature Sample Storage: A Comparative Analysis of Space Efficiency, Power Consumption, Labor Efficiency, Running Costs, and Carbon Emissions
Phd Cristiana Bercea, Mr Dean Montano
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96: Inflammation-Related Protein Variants and Their Impact on Short-Term Functional Outcomes After Ischemic Stroke
Annelie Angerfors[1], PhD Björn Andersson[2], PhD Michael Chong[3], PhD Tara Stanne[1], Prof, PhD, MD Christina Jern[1,4]
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97: Helicobacter Pylori Infection and Alzheimer's Disease Risk: The Norwegian HUNT Cohort Study
Pieta Tasnim Kelsey[1], PhD Brooke N Wolford[1], Prof Bjørn Olav Åsvold[1], Prof Håvard K Skjellegrind[1,2]
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98: Variation in the Causal Influence of Body Mass on Common Diseases Across a Lifetime
Torgny Karlsson[1], Fatemeh Hadizadeh[1], Mathias Rask-Andersen[1], Daniel Schmitz[1], Åsa Johansson[1]
[1]Uppsala University

99: Challenges in Validating Small RNA Models for Lung Cancer Prediction
PhD Luca Pestarino[1,2], PhD Renée T. Fortner[2,3], Professor Therese N. Nøst[4,5], PhD Yannis Fotopoulos[6], PhD Ilona Urbarova[4], Professor Oluf D. Røe[7], PhD Hilde Langseth[2,8], Professor Trine B. Rounge[2,9]
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100: Association of Plasma Brain-Derived Tau with Long-term Cognitive Outcome After Ischemic Stroke
Sofia Klasson[1], PhD Tara Stanne[1], MD Lukas Holmegaard[2], MD, Msc Fernando Gonzalez-Ortiz[3], Prof Henrik Zetterberg[3], Phd Hans Samuelsson[3], MD, Phd Katarina Jood[3], Prof Kaj Blennow[3], MD, Phd Christina Jern[3]
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101: Age-Related Changes in Adiposity and Disease Risks: a Longitudinal and Prospective Study in the UK Biobank
Mathias Rask-Andersen[1], Phd Valeria Lo Faro[1], Phd Torgny Karlsson[1], Phd Åsa Johansson[1]
[1]Uppsala University

103: A Wroclaw citizens health profile: First conclusions from PICTURE cohort studypos
Mrs Magdalena Krupinska[1], Prof Agnieszka Matera-Witkiewicz[1], PhD Katarzyna Połtyn-Zaradna[2], Prof Katarzyna Zatonska[2], Prof Katarzyna Kilis-Pstrusinska[3], Prof Tomasz Zatonski[4]
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104: Safer pregnancies in rheumatic disease - applications of RNA-sequencing
Hilde Julie Lien[1], Dr Tina T. Pedersen[2], Bente Jakobsen[3], Arnar Flatberg[4], Phd Konika Chawla[5], Prof Pål Sætrom[6], Dr Mona H. Fenstad[7]
[1]NTNU, [2]St. Olavs hospital, [3]St. Olavs hospital, [4]NTNU, [5]NTNU, [6]NTNU, [7]St. Olavs hospital

105: The Dutch BBMRI-node as part of the national health and life science data infrastructure Health-RI
Peggy Manders, Jörg Hamann, Lucie Kulhánková, Robin Verjans, Janet Vos, René Oostergo, Gerrit Meijer
[1]Health-RI / BBMRI.nl

106: DISRUPTOR Project: national concept of medicine 4.0 based on Regional Digital Medicine Centres pos
Agnieszka Matera-Witkiewicz[1], Iwona Chomiak-Orsa[2], Maciej Pondel[2], Agnieszka Siennicka[3]

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107: The Data Warehouse Project – FAIR biodata from the population-based Janus Serum Bank
Marie Udnesseter Lie[1], Tove Slyngstad[1], Jan Ivar Martinsen[1], Marianne Lauritzen[1], Katarina Baumgarten Skogstrøm[1], Hilde Langseth[1,2]
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108: EU Horizon Europe: REACT – Respiratory host pathogen interaction – Setup of a prospective sample collection in Denmark
Nina Drøjdahl Ryg[1], Maria Vistrup-Parry[1], Karina Meden Sørensen[1], Susanne Dam Poulsen[3], Morten Rasmussen[2], Ria Lassaunière[2], Louise Bering Pedersen[2], Amanda Bolt Botnen[2], Sofie Hørlyck[2], Máiréid Bull[2], Magdalena Malgorzata Utko[4], Lydia Viekær[1], Catrine Hansen[1], Ulrikka Nygaard[5], Sine Reker Hadrup[6], Signe Koggersbøl Skadborg[6], Ramona Trebbien[2]
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109: Impact of hemolysis on circulating miRNA in fresh and biobanked Janus Serum Bank samples
Prof Trine B. Rounge[2], Katarina Skogstrøm[1], Mrs Marianne Lauritzen[1], Phd Hilde Langseth[1]
[1]Department of Research, Cancer Registry of Norway, Norwegian Institute of Public Health, [2]Center for Bioinformatics, Department of Pharmacy, University of Oslo

110: Professionalizing biobanking in Veterinary Medicine
Kristin Sæbø Pettersen[1], Anna Karin Germundsson Hauge[1], Lars Magnus Homstvedt[1], Kristin Udjus[1], Simona Cancar[1], Rachid Fathi[1], Øivind Øines[1]
[1]Norwegian Veterinary Institute

111: Should it stay or should it go? -Assessing the value of legacy collections
Karina Standahl Olsen[1], Runa Borgund Barnung[1], Morten Rafdal[1], Kristin Sørensen[1]
[1]Core Facility for Biobanking, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway

113: Polygenic prediction of cardiorespiratory fitness: The HUNT study
Marie Klevjer[1], Mr Karsten Øvretveit[1], Prof Ben Brumpton[1], Prof Ulrik Wisløf[1], Prof Kristian Hveem[1], Prof Anja Bye[1]
[1]NTNU

114: Bologna Neuroscience Biobank: towards a 2.0 model for multidisciplinary harmonized Neuroscience multi-omic researchpos
Francesco Colaci[1], Prof Raffaele Lodi[1,2]
[1]Neuroscience Biobank of Bologna (BNB), IRCCS Istituto delle Scienze Neurologiche di Bologna, [2]Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna

116: Best Practice for Norwegian Biobanks (Beste praksis for norske biobanker) - 3rd version
Liv Paltiel[1], Phd Turid Eide[1], Mrs Elsa Roland[1], Mr. Vegard Marschhäuser[2]
[1]Oslo University Hospital, [2]Norwegian University of Science and Technology

117: Establishing versatile urine biomarker analyses on a chemiluminescence platform at HUNT Biobank

Nina Hammer, Rita Skjærvø, Therese Haugdahl Nøst[1], Lidija Klubicka, Trine Govasli Altø, Stein Hallan, Marit Næss
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118: Implementing digital droplet PCR analyses of methylated circulating tumor DNA (ct-DNA) at HUNT Biobank
Lise Norøy, Eivor Laugsand, Renathe Haugdahl Nøst, Trine Govasli Altø, Marit Næss, Therese Haugdahl Nøst
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119: Ensuring quality and quantity of DNA in the sample collections at HUNT Biobankpos
Kristin Schei Sætermo, Ann Helen Røstad, Kirsti Kvaløy, Erik R Sund, Marit Næss, Therese Haugdahl Nøst
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120: The moderating role of educational attainment on genetic differences in 19 complex diseases in Finland and the United Kingdom
Fiona Alysa Hagenbeek[1], Anne Richmond[2], Brooke Wolford[3], Max Tamlander[1], Kira Detrois[1], Zhiyu Yang[1], Tuomo Hartonen[1], Daniel McCartney[2], Riccardo Marioni[2], Pekka Martikainen[4,5], Nina Mars[1,6], Andrea Ganna[1,7], Samuli Ripatti[1,8]
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121: canSERV – providing cutting edge cancer research services across Europepos
Manuela Pausan[1], Mrs Judit Balogh[1], Prof John Eriksson[2], PhD Serena Scollen[3], Prof Vitor Martins dos Santos[4], Prof Enzo Medico[5], PhD Bahne Stechmann[6], PhD Michael Hagn[7], PhD Corinna Brockhaus[8], PhD Stéphane Lejeune[9], PhD Zisis Kozlakidis[10], PhD Michael Raess[11], PhD Nicolas Pade[12], PhD Marta del Alamo[13], MD Elena Garralda[14], PhD Emanuela Oldoni[15], Prof Nelson Lima[16], Mrs Martha Gilbert[17], Prof Karen Kirkby[18], Prof Jens K. Habermann[1]
[1]BBMRI-ERIC, [2]EURO-Bioimaging, [3]ELIXIR/EMBL, [4]Wageningen University representing IBISBA, [5]Universita degli Studi di Torino representing EuroPDX, [6]EU-OPENSCREEN, [7]ARTTIC, [8]Instruct ERIC , [9]EORTC, [10]IARC/WHO, [11]INFRAFRONTIER, [12]EMBRC, [13]ECRIN, [14]Fundacio Privada Institut D'Investigacio Oncologica De Vallhebron representing Cancer Core Europe, [15]EATRIS , [16]Universidade do Minho representing MIRRI, [17]ttopstart, [18]University of Manchester representing ARIE

122: Genome-wide association studies in FinnGen and the UK Biobank highlight genes involved with both nociceptive and neuropathic pain
Martin Broberg[1], PhD FinnGen[1], PhD Hanna Ollila[1,2]
[1]Institute For Molecular Medicine Finland, [2]Center for Genomic Medicine, and Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School

123: Premature Deaths, Incomplete Answers: Unmasking the Full Picture of Mortality in Danish Neonates

Paula L. Hedley[1,2], MD, PhD Ulrik Lausten-Thomsen[1,3], PhD Atsumi Hirose[4,5], Prof Michael Christiansen[1,2,6]

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124: Incidence trends and risk factors for Legg-Calve-Perthes disease: A Danish nationwide register-based study using publicly available data

Paula L. Hedley[1,2], MD, PhD Ulrik Lausten-Thomsen[1,3], PhD Kristin M. Conway[2], Prof Klaus Hindsø[4], Prof Paul A. Romitti[1,2], Prof Michael Christiansen[1,2,5]

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125: Is genetic liability to higher muscle strength a proxy for intrinsic capacity to resist age-related pathologies and mortality?

Elina Sillanpää[1], Kaisa Koivunen[1], Teemu Palviainen[2], Jaakko Kaprio[2], Urho Kujala[1], Katja Waller[1], Laura Joensuu[1], Päivi Herranen[1]

[1]University of Jyväskylä, Faculty of Sport and Health Sciences, [2]Institute for Molecular Medicine Finland

126: Environment, lifestyles and health – A recall pilot study in the Central Finland biobank

Elina Sillanpää[1], Suvi Ravi[1], Pauli Wihuri[2], Kirsikka Aittola[3], Eija Laakkonen[1], Merja Rantakokko[1], Tiina Jokela[4], Tiina Föhr[1]

[1]University of Jyväskylä, Faculty of Sport and Health Sciences, [2]Finnish Biobank Co-operative, [3]University of Eastern Finland, [4]Central Finland Biobank

127: Integrating Radiomic Features from MRI with Clinical Variables to Predict Prostate Cancer Recurrence.

Selma Bozorgpana[1]

[1]NTNU

128: Danish Primary Care Trajectories

Jessica Xin Hjaltelin[1,3], PhD Peter Holm[1], Mr Samuel Cadell[1,3], Mr Troels Siggaard[1], PhD Isabella Friis Siggaard[1], Mr Christian Holm Johansen[1,3], PhD Alexander Wolfgang Jung[1,3], Prof Laust Hvas Mortensen[3,4], Prof Søren Brunak[1,2,3]

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129: Age of autism diagnosis and family wellbeing: exploring the association and its confounding factors in the MoBa cohort.

Bernt Damian Glaser[1], Dr Laurie Hannigan[1], Dr Daniela Bragantini[1], Stian Orm[7], Morgan Morgan[8], Prof Alexandra Havdahl[1]

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University of Bristol, [7]Department of Psychology, Inland Norway University of Applied Sciences, [8]Department for Brain and Cognitive Development, Birkbeck University of London

130: Joint Effects of Recurrent Copy Number Variants and Polygenic Scores on the Risk of Psychiatric Disorders in iPSYCH2015 case-cohort

Morteza Vaez[1], MSc Simone Montalbano[1], Phd Jesper R. Gådin[1], Dr. Ryan K. Waples[1], iPSYCH Collaborators[2], Phd Dorte Helenius[1,2], Prof Thomas Werge[1,2,3], Phd Andrew J. Schork*[1,2], Phd Andres Ingason*[1,2]
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131: Mitochondrial DNA Haplogroup Variation and Psychiatric Disease

Mr Jonas Bybjerg-Grauholm[1], Mr Christian Hagen[1], Dr Paula Hedley[1], Michael Christiansen[1]
[1]Statens Serum Institut

132: Maintaining Sample Integrity During Repeated Freeze/Thaw Cycles

Leigh Carter, Alexis MacLeod
[1]Azenta Life Sciences

133: Detection of structural brain aberrations in patients with dementia using explainable artificial intelligencepos

Esten Høyland Leonardsen[1], Dr Thomas Wolfers[1,2], Prof. Lars T. Westlye[1], Prof. Yunpeng Wang[1]
[1]University of Oslo, [2]University of Tübingen

134: Branched-chain organic acidurias/acidemias in Denmark from 1996 – 2020: A nation-wide register-based case-cohort study of trends in birth prevalence, pregnancy complications and consequences of newborn screening

Michael Christiansen[1], Dr Paula Hedley[1], Dr Ulrik Lausten-Thomsen[2], Prof Mette Nyegaard[1]
[1]Statens Serum Institut, [2]Copenhagen University Hospital

135: Full-exome analysis of xanthine dehydrogenase gene: possible implications for tuberculosis pharmacogenetic studies.

Anda Viksna[1,2], Lauma Freimane[3], Viktorija Ulanova[1], Agnija Kivrane[1], Eduards Sevostjanovs[4], Solveiga Grinberga[4], Iveta Ozere[1,2], Renate Ranka[1]
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136: Missense variant in GPR101 in X-chromosome predisposes to sleep fragmentation (in sex specific fashion)

Viola sofia Helaakoski[1], Jonathan Blumenthal[1], Phd Samuel Jones[1], FinnGen, Phd Taru Tukiainen[1], PhD Martin Broberg[1], Hanna Ollila[1,2,3,4]
[1]Institute for Molecular Medicine Finland (FIMM), [2]Broad Institute of MIT and Harvard, [3]Center for Genomic Medicine, Massachusetts General Hospital, [4]Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School

137: Quantitative estimates of microbiome heritability and their implications

Andrew Hayden Morris[1], Prof Brendan J. M. Bohannan[2]
[1]University of Oslo, [2]University of Oregon

138: Applications of COSGAP: COntainerized Statistical Genetics Analysis Pipelines

Espen Hagen[1], Dr. Bayram C. Akdeniz[1], Dr. Oleksandr Frei[1], Mr. Tahir T. Filiz[1], Dr. Vera Fominykh[1], Prof. Ole A. Andreassen[1]
[1]University of Oslo

139: HLA imputation in the Norwegian Mother, Father, and Child Cohort
Kinnie LeRoy, Matthieu Leveau, Marc Vaudel, Per Magnus, Ellen Christine Røyrvik[1]
[1]Folkehelseinstituttet, University of Bergen

140: Low polygenic risk score for autoimmune Addison's disease identifies misdiagnosed cases of monogenic primary adrenal insufficiency
Maribel Aranda[1], Ileana Ruxandra Botusan[1,2], Venuja Fernando[1], Ellen Christine Røyrvik[3,4,5], Anette Susanne Bøe Wolff[3,4,6], Stefan Johansson[3,7], Eystein Sverre Husebye[1,3,4,6], , The Swedish Addison Registry Study Group, Sophie Bensing[2,8], Olle Kämpe[1,2,4], Daniel Eriksson[1,9]
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141: From multi-omics to better health – Managing the biological data resource in the Norwegian Mother, Father and Child Cohort Study (MoBa)
PhD Even Birkeland[1], Phd Kishan Kumar Chudasama[2], Ragnhild Valen[1], Phd Johanna Lucia Thorbjørnsrud Nader[2]
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142: The role of biobank in monitoring the immune system of hemato-oncological patients undergoing modern immunotherapy
Lucie Broskevičová[1,2], Jana Klepáčová[1], Hana Križňanská[1], Prof Roman Hájek[1,2]
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4: Genetic liability to sedentary behaviour increases the risk of sedentariness and cardiovascular disease incidence: Evidence from the FinnGen cohort with 293,250 individuals

Laura Joensuu[1], Kaisa Koivunen[1], Anna Kankaanpää[1], Niko Tynkkynen[1], Teemu Palviainen[2], Jaakko Kaprio[2], Marie Klevjer[3], Karsten Øvretveit[4], Ulrik Wisløff[3], Anja Bye[3], Ulf Ekelund[5,6], Elina Sillanpää[1,7]
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Cardiometabolic Disorders II: Risk Predictors, Cosmos 1-2, september 11, 2024, 15.45 - 17.00

Background
Energy-saving sedentary behaviour may be an evolutionarily selected trait that is no longer favoured in the current environment, potentially increasing population morbidity.

Purpose
What is the association between genetic liability to sedentary behaviour, sedentariness, and the incidence of cardiovascular disease (CVD)?

Methods
We developed a polygenic score to indicate genetic liability to leisure screen time (PGS LST) based on approximately 891,000 genetic variants using the SBayesR method. We thereafter tested the validity of this score against self-reported leisure screen time in the older Finnish Twin Cohort (N=2,689, 60.5±3.7 years, 54.7% women) using linear regression. We examined the associations between PGS LST and register-based records of CVDs using the Cox proportional hazards model among the FinnGen participants (N=293,250 for all CVDs, 67.0± 13.0 years, 52.3% women) and replicated analyses in an independent cohort (The Trøndelag Health Study [HUNT], N=34,849, 64.3±12.9 years, 51.6% women).

Results
Each standard deviation increase in PGS LST was associated with more self-reported LST (hours/day) (β 0.09, 95% confidence interval [0.05-0.13]), and higher risk of incident CVD (hazard ratio 1.05, [1.05-1.06]) (168,770 cases over 17,101,133 person-years). The magnitude of associations for three most common CVDs were 1) hypertensive diseases: 1.08 (1.07-1.08) and 1.10 (1.09-1.11) for men and women, respectively (56,984 and 51,056 cases, Pinteraction=0.004 for PGS LST×SEX), 2) ischemic heart diseases: 1.06 (1.05-1.07) (64,724 cases), and 3) cerebrovascular diseases: 1.05 (1.04-1.06) (34,170 cases). Associations replicated with almost identical effect sizes in the HUNT cohort, except for cerebrovascular diseases in women.

Conclusions
A higher genetic liability to sedentary behaviour is associated with more sedentariness and a greater risk of developing CVD, although the effect sizes remain relatively small when using PGS. Genetics is a noteworthy underlying factor for both sedentary behaviour and CVD risk at the population level.

Funding
Funded by the Research Council of Finland (to ES).

6: A genome-wide association study in European advanced cancer patients treated with opioids identified variants regulating the expression of OPRL1 as possible modulators of pain intensity.

Francesca Minnai[1,2], Morena Skhodra[3,4], Sara Noci[5], Pål Klepstad[6,7], Stein Kaasa[3,8], Oscar Corli[9], Marco Cesare Maltoni[11], Augusto Tommaso Caraceni[4,12], Francesca Colombo[1]
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Cancer pain causes suffering and lowered quality of life, thus advanced cancer patients often require analgesic therapy. Opioids of step III of the WHO-defined analgesic ladder are the standard of care for the treatment of cancer pain. However, 20-30% of patients do not receive adequate pain relief from opioids. Literature suggests that genetics plays a role in predisposing patients to a good or poor response to opioids and, herein, we investigated it by performing a genome-wide association study (GWAS).
Methods: We individually genotyped 2,060 European advanced cancer patients treated with morphine, buprenorphine, fentanyl, and oxycodone. We performed a whole-genome regression model (using REGENIE software) between genotypes and the opioid response phenotype, defined as a numerical score measuring pain intensity based on patients' responses to the Brief Pain Inventory Questionnaire.
Results: The GWAS identified five non-coding variants on chromosome 20 at P-value < 5.0x10-8. For all of them, the minor allele was associated with a lower pain intensity. These variants were intronic of PCMTD2 gene and were 200 kbp downstream of OPRL1, the Opioid Related Nociceptine Receptor 1. Interestingly, four of them acted as expression quantitative trait loci, modulating the expression of OPRL1, according to eQTLGen database.
Conclusion: This is the largest GWAS performed in this field, so far. Our results strengthen the evidence for a role of genetics in opioid response. Further functional analyses are needed to validate the results obtained and to understand the biological mechanism underlying the observed associations.

7: Associations between inflammation markers and breast cancer risk in the HUNT population

Julia Debik[1]
[1]NTNU

Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background:
Breast cancer is the most common cancer among women worldwide, with an increasing incidence rate. A better understanding of the complex biology leading to breast cancer formation is crucial for disease prevention, while early detection is important for a good prognosis. The aim of the study was to investigate associations between inflammatory and metabolic markers in serum and the long-term risk of developing breast cancer.

Methods:
We identified 352 women from the Trøndelag Health Study (the HUNT study) who donated blood in the period 2006-2008 and had developed breast cancer within a 15-year follow-up period. Using Olink Target 96 inflammation panel, 92 inflammation related proteins were measured in the serum samples of these women, and an equal number of age-matched controls that remained breast-cancer free in the follow-up period. In addition, 249 metabolic measures through the Nightingale Health's metabolic platform were available for a subset of these women. Using logistic regression, we tested for associations between the measured markers and long-term breast cancer risk.

Results:
Four proteins (IL-15RA, CX3CL1, TNFRSF9, and FGF23) were significantly associated ($p<0.05$ after Benjamini-Hochberg correction for multiple testing) with risk of breast cancer within two years after sample collection, but not when investigating longer-term breast cancer risk > 2 years. The predictive ability of these markers was tested using an extreme gradient boosting algorithm (XGBoost) in a multivariate model, showing significant, but weak classification of future breast cancer.

Conclusions:
We saw evidence suggestive of an anti-tumor immune response up to two years prior to diagnosis. This panel of inflammation biomarkers, by themselves, is however not sufficient to accurately predict long term breast cancer risk.

8: National Patient Participation within Biobank Sweden

Marija Armus, PhD Linda Lindskog, PhD Sonja Eaker Fält, Alexander Hertzberg
[1]Biobank Sweden

Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction
The Swedish Biobank Act is recognized globally for its strong protection of citizen integrity as sample donors. To support sustainable biobanking and compliance to laws and regulations, Biobank Sweden (a national biobanking infrastructure) is starting a new initiative to increase patient involvement within the network. The initiative emphasizes the importance of health literacy through proper and distinct information and communication.
Methods
The initiative involves comprehensive mapping exercises and explores various forms of collaboration between stakeholders. The conclusions in the report “Collaboration 2.0: Sustainable collaboration for value and innovation” (2023) will be used as guidance. An initial phase includes the involvement of the European Patients´ Academy on Therapeutic Innovation (EUPATI), development of patient-oriented information materials and engagement with patient representatives and organizations.
Results
Dialog meetings and workshops will be conducted to identify relevant content for education and communication. Patient representatives will be actively involved in reviewing materials to ensure accessibility and relevance. A new education program will be integrated into a digital learning platform and launched for healthcare, academia, industry and patient organizations. The work also aims to include the patient perspective in research on individuals unable to make decisions for themselves at the point of care and improve processes for better patient-centered outcomes.
Discussion
By actively involving patients in the biobanking segment, Biobank Sweden aims to increase awareness and understanding of the significance of human biological material in research and the development of healthcare. Patient participation and patients´ health literacy is vital for ethical and sustainable biobanking practices and improved patient outcomes.
Reference list:
Claerborn, A., Degsell, E., Kannisto, K., Haag, M., Friedman, M., Riggare, S., & Juran, S. (2023). Patient and next-of-kin collaboration for better research and healthcare. Collaboration 2.0: Sustainable collaboration for value and innovation (Report Samverkan 2.0). Riksförbundet Sällsynta diagnoser, Nätverket mot cancer, Regionalt cancercentrum Stockholm-Gotland, Forum spetspatient, Biobank Sverige, Genomic Medicine Sweden och ATMP Sweden. Patient and next-of-kin collaboration for better research and healthcare (biobanksverige.se)

9: Assessing the susceptibility of celiac disease by polygenic risk scores: analysis of a population-based cohort, the HUNT study.

Mohammad Sayeef Alam[1,2], Rebecka Hjort[1,2], Kristian Hveem[1], Knut E. A. Lundin[3,4], Iris H. Jonkers[5], Ludvig M. Sollid[4,6], Eivind Ness Jensen[1,2,7,8]

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Selected young researchers' talks, Cosmos 1-2, september 12, 2024, 13.00 - 14.15

Introduction: Despite diagnostic advances in celiac disease (CeD), many patients remain undiagnosed. CeD has well established genetic risk factors in the leukocyte antigen (HLA) loci. The goal of the study was to provide susceptibility estimates for CeD subgroups using polygenic risk score (PRS) beyond the HLA loci.

Methods: In the population-based HUNT study in Norway, 52,588 adults underwent CeD screening via serology with diagnosis confirmed by histology (revealing 465 incident [Marsh 3] and 230 potential [Marsh 1/2] cases). Additionally, 377 known CeD cases were identified from medical registries. We reproduced a previously published PRS of CeD (228 SNPs) using the PRS-cs tool. All analysis were adjusted for age, sex, genotyping batch and 20 principal components.

Results: The PRS could effectively distinguish between incident and prevalent cases from controls, with area under receiver operating characteristic curves at 83.8% and 83.5%, respectively, superior to potential cases (68.8%). For every standard deviation increase in the PRS, the odds increased 3.4-times (95% confidence interval [CI] 3.1-3.8) for confirmed (incident and prevalent) and 1.8-times (CI 1.6-2.1) for potential cases. Individuals in the top vs remaining decile of the PRS had 8.4-times (CI 7.3-9.7) higher odds of CeD. The proportion of variation explained by the PRS was 20.9% (CI 17.2%-25.6%) from HLA and 1% (CI 0.2%-2.3%) from non-HLA.

Conclusions: Incorporating non-HLA variants slightly enhanced identification of CeD beyond HLA variants alone, highlighting the potential of genetic risk stratification, integrating both HLA and non-HLA variants to pinpoint high-risk individuals.

13: The IRX1 locus is associated with celiac disease: results from a screened population-based cohort, the HUNT study.

Mohammad Sayeef Alam[1,2], Rebecka Hjort[1,2], Laurent F Thomas[1,3,4], Ben Brumpton[1,2], Kristian Hveem[1], Knut E A Lundin[5,6], Iris H Jonkers[7], Ludvig M Sollid[6,8], Eivind Ness Jensen[1,2,9,10]
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction: Previous studies have uncovered genetic loci associated with celiac disease (CeD), within both the human leukocyte antigen (HLA) and the non-HLA region. Yet, half of the genetic variation remains unexplained. This study aims to investigate novel loci associated with CeD in a screened population, mitigating potential selection-bias from prior case-control studies.
Methods: Utilizing data from the HUNT study in Norway, we screened 52,358 adults (>20 years) for CeD using serology, identifying 465 incident biopsy-confirmed cases. Additionally, 377 prevalent cases were identified through hospital journal searches. Genotyping of 373,185 SNPs was performed using four Illumina HumanCoreExome arrays. Imputation, using the Haplotype Reference Consortium panel, resulted in approximately 24.9 million variants, post quality control. A genome-wide association study (GWAS) was performed using SAIGE, and functional mapping and pathway enrichment analysis was conducted using FUMA.
Results: Out of six independent associations reaching genome-wide significance and with a minor allele count >10, we identified one known (IRX1) and five novel (EML6, BCL11A, ABCA12, LRFN2, and MED13) loci. We replicated 49 out of over 80 known loci from previous GWASs, with REL, ASHA2, IL18RAP, IL18R1, IL18RL1, IL18RL2, LPP, PFKFB3, PRKCQ, CIITA, SOCS1, and CLEC16A reaching suggestive significance levels (5×10^(-8)≤P≤5×10^(-6)).
Conclusion: The strongest evidence for an association was observed at IRX1, warranting further studies to validate this finding. Notably, the IRX1 loci has also been associated with other autoimmune diseases such as rheumatoid arthritis.

14: Genetics correlations of ME/CFS

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and debilitating medical condition that is characterized by profound fatigue, post-exertional malaise, cognitive impairment, unrefreshing sleep as well as broad range of other multisystemic symptoms. Despite its rather high prevalence (estimates ranging between 0.1 % to 2.5 %) the biological etiology of the disease is poorly understood, there are no biomarkers or laboratory tests to support the diagnosis.

Our goal was to understand the genetic etiology and risk factors that contribute to ME/CFS. We used linkage disequilibrium score regression analysis to examine genetic correlations between ME/CFS and diseases with dysautonomia component, sleep traits, neuro-psychiatric traits and autoimmune diseases. We explored also possible causal relationships utilizing Mendelian randomization.

We discovered significant positive correlations between ME/CFS and dysautonomia related diagnoses (Raynaud, hEDS, Fibromyalgia and Lyme disease), sleep traits (insomnia, evening chronotype and napping), neuropsychiatric diagnoses (anxiety, neuroticism and depression) and immune diseases (asthma and Sjögren's disease). Mendelian randomization analysis suggested a causal relationship between immunity (cancer and allergic diseases), evening chronotype, and depression as risk factors for ME/CFS ($P < 0.05$).

Our findings indicate a correlation between ME/CFS and sleep, psychiatric and immune traits and diseases with dysautonomia with a possible causal risk from chronotype and depression to ME/CFS. Future studies will likely elucidate the biological mechanisms behind ME/CFS.

15: Time-series assessment of 15 serum biochemical analytes to explore storage time impact up to 9 years at -25 °C

Steffan Daniel Bos[1,2], Marianne Lauritzen[1], PhD Nathalie C Støer[1], Associate Professor Olav Inge Klingeberg[3,4], PhD Hilde Langseth[1,5]
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Implementing Biobank Standards, Cosmos 3AB, september 11, 2024, 15.45 - 17.00

Introduction:
Biorepositories are important resources in medical research for better understanding the cause and development of diseases.Serum analytes assessed in such biorepositories represent low-invasive, low-cost biomarkers that may reflect an individual's status for a wide range of biological pathways. In the Janus Serum Bank, over 700 000 serum samples from 318 628 donors have been stored at -25 °C for up to 50 years. There is limited knowledge on how different categories of serum analytes respond to storage at this temperature over time.
Aim:
To explore the (in)stability of different serum analytes at -25 °C over prolonged storage times up to 9 years.
Materials and Methods:
We included blood samples from 40 consenting volunteers. Samples from each donor were processed to 17 serum aliquots of 1 ml in 1,5 ml screwcap vials and stored at -25 °C. One fresh sample was subjected to biochemical analyses at baseline, followed by measurements of the selected analytes after 3, 6, 12, 24, 36, 72 and 108 months in the freezer. Using a Cobas Biochemical analyzer a panel of 15 analytes was assessed comprising proteins (albumin, immunoglobulin G & C-reactive protein); enzyme (aspartate aminotransferase); water soluble components (creatinine, glutamine, glucose, bilirubin, urea, sodium & potassium), hormones (testosterone & thyroid stimulating hormone), lipids (cholesterol & triglycerides) and vitamin (B12). All analyses were performed in a facility accredited according to NS-EN ISO 15189. After thawing at each timepoint, samples were analyzed in a single batch with internal controls for each assay. For each analyte, the biochemical data was tested for adhering to an approximate normal distribution, and where relevant the data was transformed to approximate normal distribution. Each analyte was compared across the storage times with the 3-month sample used as the reference sample. We used descriptive statistics (median and interquartile range), one-way ANOVA with repeated measurement and pairwise t-tests or Wilcoxons' non-parametric test. Multiple testing was adjusted for by Bonferroni correction. Analyses were performed using R4.3.2.
Results:
For 40 donors, we obtained biochemical measurements for 15 serum analytes at eight timepoints after freezing. Some of the analytes (e.g. triglycerides and vitamin B12) showed measured values in line with the 3 months timepoint, other analytes (e.g. glucose and thyroid stimulating hormone) showed a declining trend in the measured values (Figure 1). For most of the repeated measurements we observed significant different values as compared to the 3-month reference value.
Conclusion:
Certain biochemical analytes are affected by storage time and temperature. Further, we cannot exclude technical and/or batch effects attributable to assay lots, machine calibrations etc. Studies using biorepositories should consider that storage may impact measured values. Inclusion of samples from matched controls that experience similar storage time and conditions will increase the value of biorepositories.

17: Towards a more general consent for the use of patients' biological material and health information for medical research - The patient perspective

PhD Rebeca Bruu Carver[1], PhD Isabelle Budin-Ljøsne[1], Matthias Kolberg[2], Wenche Reed[2], Øyvind Mikkelsen[3], Solveig Kvam[3], Jostein Halgunset[3], Birgitte Wirum Sand
[1]Norwegian Institute of Public Health, [2]Oslo University Hospital, [3]St. Olav's hospital, [4]Directorate of Labour and Welfare

Selected Biobank Abstracts, Cosmos 3AB, september 12, 2024, 11.00 - 12.00

Biological material and health information from patients are valuable for medical research. Under a "broad" consent model, hospital patients in Norway can consent to their biological material and health information being stored in research biobanks and used for "specific, broadly defined research purposes" within a specified medical research area, but not for medical research in general. Patients must provide new consent each time researchers wish to use their material in other medical research areas. This study investigated patient representatives' views on general consent for medical research without limitation to specific research purposes, preferences for the storage of biological samples, consent collection and timing, and factors motivating or hindering consent. A digital, anonymous survey was shared with patient representatives from patient advisory councils at national hospitals in Norway, who answered the survey on behalf of patients. 157 representatives completed the survey (response rate of 41%). A majority (66.2%) supported general consent for medical research and the use of surplus material for medical research in general (63.7%) without limitation to specific research purposes. A minority (35%) supported the use of surplus material without being informed. 65% agreed that biological samples could be stored with no time limitation. Most (56%) believed patient consent should be collected before the patients meet up at the hospital and recommended offering patients the possibility to choose between digital or paper consent (70.7%). Factors motivating consent included the desire to contribute to medical research (89.8%) and faith in scientific progress (24.2%). Main hindrances included the fear that health information may be used for other purposes than research (49%), uncertainty regarding research uses (43.9%) and lack of information (31.8%). A move toward general consent to medical research may better comply with patients' wishes and maximize research potential.

From Estonian biobank to practice: undiagnosed adult NDD-CNV carriers present complex health effects and express contentment to learn about their genetic finding.

Marili Palover[1], Margit Nõukas[1], Anu Reigo[1], Helene Alavere[1], Liis Leitsalu[1,2], Alexandre Reymond[3], Neeme Tõnisson[1,2], Katrin Männik[4]

[1]University of Tartu, Institute of Genomics, Estonian Biobank, [2]Tartu University Hospital, Genetics and Personalized Medicine Clinic, [3]University of Lausanne, Center for Integrative Genomics, [4]Health 2030 Genome Center, Foundation Campus Biotech Geneva

Neuropsychiatric disorders and Alzheimer's Disease, Cosmos 1-2, september 10, 2024, 15.30 - 17.00

While pioneering national genomic medicine initiatives focus on returning individual risk predictions for medically actionable monogenic and common diseases, studies on the psychosocial impact and evidence-based recommendations on reporting genetic data to citizens at high risk of complex clinical phenotypes, e.g. neurodevelopmental disorder CNVs (NDD-CNVs) are missing. This lack of knowledge is present although adult NDD-CNV carriers tend to belong to a vulnerable fraction of the society as we and others have shown that a significant portion of them have long-term physical and mental health problems and lower socioeconomic status associated with these variants.

We aimed (i) to set up a model framework to deliver genetic findings and provide assistance to NDD-CNV carriers at high genetic risk for complex disorders, (ii) to collect data on at-risk individuals' expectations, experience and the psychosocial impact of adult-age genetic finding, and (iii) to compare these with results from other Estonian biobank (EstBB) feedback projects.

We selected carriers of 16p11.2 and 16p12 NDD-CNVs of the EstBB to establish a framework for returning CNV findings to population biobank participants and to evaluate psychosocial impact of receiving this information. The two-visit protocol contains validation of the NDD-CNV finding at two time-points, developmental and health interviews, blood biochemistry measures to complement EHR data, genetic counselling customized according to each participant's existing health conditions, followed by questionnaires on psychosocial aspects of risk disclosure at two time-points.

Across three selected NDD-CNVs, 77 of 168 carriers (46%) consented for return of results. The majority (89%) of carriers presented health conditions characteristic of the associated genomic disorders, i.e. neuropsychiatric and -developmental problems (43%), disorders of female reproductive health (53%), gastrointestinal disease (67.1%) and speech disorders (51.3%). Only 2 (2.6%) participants were previously aware of their genetic finding through offspring cascade testing.

Preliminary analysis of carriers who received unexpected genetic information (data from 75 out of 77 participants) showed that almost all of them (96%; 74/77) appreciated being contacted (2 were unsure and one did not answer). The participants felt that the information received was sufficient (99%; 76/77), understandable (92%; 71/77) and gave them relief (83%; 64/77). Participants felt calm (94%; 72/77) and did not show increased concern (88%; 68/77) or anxiety (86%; 66/77) after disclosure. Evaluation of long-term (>6 months) impact is currently ongoing. The preliminary results obtained to date (19 of 77) indicate participants remaining calm (79%; 15/19), not anxious (79%; 15/19) or worried (74%; 14/19). However, initial data indicate slightly different tendencies in long-term feelings of confusion and concern between carriers of syndromic CNVs (e.g. 16p11.2 del) and CNVs with more variable expressivity (e.g. 16p12 del). Additional analyses on individual patterns, questions about emotions and regrets are in progress.

In conclusion, NDD-CNVs affect health and socio-economic outcomes in the general population but, despite their strong impact, are underdiagnosed in adult population. Carriers of such rearrangements who choose to consent for receiving the information appreciate being contacted. For a large majority of carriers, learning the genetic origin of their CNV-related health problems does not cause negative psychosocial impact.

19: Blood proteome profiling using proximity extension assay in patients with acute myeloid leukemia

Emil Johansson[1], María Bueno Álvez[1], PhD / MD Sören Lehmann[2,3], Prof Tobias Sjöblom[4], Prof Ulf Gyllensten[4], Prof Adil Mardinouglu[5,6], Prof Mathias Uhlén[1,7], Phd Fredrik Edfors[1]
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Acute Myeloid Leukemia (AML) is the most common form of acute leukemias in adults. Plasma proteomic profiling represents an attractive way to assess biomarkers and screen for early diagnosis in malignant diseases, but studies remain scarce in AML. This study was conducted by analyzing 1 463 plasma proteins in 52 AML patients at diagnosis using the Olink Explore 1536 platform. Both differential expression analysis and feature selection by machine learning were applied to find the most significant proteins to distinguish AML from 867 healthy individuals and 1 734 patients of varying cancer types, including different hematological malignancies. The analysis identified several proteins with significant altered in AML patients as compared to multiple controls, such as, FLT3, FLT3LG, EPO, PGLYRP1, LCN2, FCGR3B, TNFRSF10C and CDH17.

20: Cohort profile update: The Norwegian Mother, Father and Child Cohort Study

Maria Aamelfot[1], PhD Dana Kristjansson, PhD Ragnhild Brandlistuen
[1]Norwegian Institute of Public Health

Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a large ongoing prospective population-based cohort aimed at studying causes of diseases. As a birth cohort with trio data, MoBa offers a framework for studying environmental factors, by self-reported measurements or biomarkers, during pregnancy and their effect on child development and health status during adolescence and adulthood. The family-centric design enables nuanced analyses and insights on intergenerational dynamics. It allows for the exploration of complex interactions between genetic predispositions, environmental influences, and social factors, ultimately advancing our comprehension of health and disease trajectories across a generation.

Between 1999 and 2008, pregnant women and their partners were invited to participate when attending ultrasound examination around 17 weeks' gestation. A total of 114 500 children, 95 000 mothers and 75 000 fathers were recruited based on consent. This includes 16 400 mothers with more than one pregnancy (i.e. siblings) and 1900 pairs of twins.

The parents responded to questionnaires on physical and mental health at regular intervals during and after pregnancy. Continued engagement with participants includes ongoing data collection efforts, particularly focusing on adolescence and young adulthood. The children respond to questionnaires from age 13. Ongoing data collections include The MoBa-Young-questionnaires at age 16-17 years, 18, 19, 20-25 year questionnaires and post-Covid19 questionnaires. This data can be supplemented by linkage to other national registries such as the Medical Birth Registry of Norway.

For detailed information on additional collections of biological material in MoBa, see abstract on other projects with collections of biological material in MoBa.

Biological samples were obtained from parents during pregnancy, and from mother and child (umbilical cord) after birth. MoBa-Bio is a repository of genetic (including epigenetic), metabolomic, and proteomic data that had been collected and stored for research use. 82% of participants have been genotyped. The MoBa biobank stores biological samples of DNA, RNA (child), whole blood, plasma, urine (mother). Teeth (child) are stored at the University of Bergen.

MoBa has yielded over 1100 publications, underscoring its substantial contributions to scientific knowledge in multiple fields. More information on the cohort may be found at www.fhi.no/moba.

21: Expanding Research Horizons: Diverse Biological Collections in the Norwegian Mother, Father, and Child Cohort Study (MoBa)

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The Norwegian Mother, Father, and Child Cohort Study (MoBa) represents a pivotal population-based pregnancy study, initiated with the primary aim of identifying causal factors - ranging from environmental toxins and infections to dietary factors and work-related stress - that can be mitigated through preventive measures. For additional insights, we refer to abstract "Cohort profile update: The Norwegian Mother, Father, and Child Cohort Study" which details the main collection's scope and purpose.

Several research projects have used MoBa as a foundational resource for selecting participants. These encompass a broad spectrum of investigations, including the effects of environmental pollution on human health, the nuances of eating disorders during pregnancy, and the seroprevalence observed in the SARS-CoV-2 pandemic, thereby illustrating the cohort's extensive applicability. Central to these endeavours, the MoBa Biobank has played a crucial role in receiving, processing, and securely storing samples for numerous MoBa-affiliated projects. Using rigorous protocols, blood, plasma, and urine samples are meticulously processed, frozen, and stored under optimal conditions. Currently, the Biobank safeguards approximately 5 million individual sample tubes, each containing precious biological material.

In total, eight MoBa projects have involved the collection of biological material, with participants providing informed consent that outlines each project's connection to MoBa. Of these, seven are directly managed by the Biobank, housed within the Department of Biobanks at the Norwegian Institute of Public Health (NIPH). Notable projects include Women's Fertility, MoBa Covid-19, The Environmental Biobank, BraPust, Language and Learning in Eight-Year-Old Children, The Autism Birth Cohort (ABC), and The Reliability Project.

Sample collection occurred across various settings, from hospitals and general practitioners' offices to specialized clinics, thereafter, transported to the Biobank for detailed processing and long-term preservation. The Biobank adheres to standardized sample handling protocols, with all pre-analytical procedures documented within the biobank inventory management system (BIMS).

Questionnaire data, genetic data, and biological material from MoBa are made accessible for research purposes upon application, in strict adherence to Norwegian law. Detailed guidance on how to apply for access to MoBa's biological material, including requirements and the application process, is available on the MoBa website (www.fhi.no/moba).

This overview not only emphasizes MoBa's instrumental role in fostering a wide array of research projects but also underscores the critical contributions of the MoBa Biobank to advancing public health research and expanding our collective knowledge. Through this enhanced collaboration, MoBa continues to be a cornerstone in the landscape of public health research, offering unparalleled insights and opportunities for discovery.

22: Mapping the familial and genetic basis of eating disorders: a comprehensive national register study of Denmark and Sweden.

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Selected young researchers' talks, Cosmos 1-2, september 12, 2024, 13.00 - 14.15

Eating disorders (EDs): anorexia nervosa (AN), bulimia nervosa (BN) and other eating disorders (OED) have a genetic underpinning and often co-occur with other mental disorders. This population-based study estimated the heritability of EDs, their familial risk and shared genetic risk between EDs and multiple mental and cardiometabolic diseases (CMD) at the population level. We used data from national registers for the entire Danish and Swedish population, including individuals diagnosed with AN, BN, and OED (n=27,390 in Denmark, n=45,724 in Sweden) and their first-degree relatives, together with birth-year matched unaffected individuals and their relatives. Individuals with a first degree relative diagnosed with an ED had a 2 to 5-fold increased risk of an ED diagnosis compared with the general population. Meta-analysed cross-country heritability estimates were h^2AN=0.37, h^2BN=0.39, and h^2OED=0.32, and comparable across countries. Genetic correlations revealed a substantial genetic overlap between AN and obsessive-compulsive disorder (OCD) (rg=0.61, p=1.19x10-54) and most mental disorders (h2 range: 0.27-0.55). We additionally observed a significant genetic correlation between BN and three CMDs. Our results confirm that all EDs have an underlying genetic component. Genetic correlations support evidence that commonly observed comorbidity patterns may be partly attributable to a shared genetic architecture between EDs and other disorders and shed light on the cardio-metabolic component of EDs.

23: Explaining biobanking using a board game

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Students are researchers of the future. Therefore, students of life sciences and medicine should have heard about and understand the basic principles of biobanking.
As an additional alternative teaching method to otherwise common lectures, seminars, practical courses, bedside teaching or others, a board game format was considered. Game based learning means to learn while gaming. The idea is to design games in such a way, that learning content can be delivered. Learning using games does not only increase the motivation but encourage deeper processing of the learning content through active engagement with the game.

For this purpose, on the one hand, the basic principles of biobanking to be learned and on the other hand, possible easy-to learn games were analyzed. For the adaption of an easy-to learn game to the principles of biobanking, several board and card games were considered. The choice fell on "The Mysterious Forest", a children board game published by iello. The game consists of three distinct phases, a) remembering items, b) picking the remembered items, c) checking whether the picked items are identical with the original items. The licensing issue was discussed with the publishers of the original game. Based on this methodology, the game was adapted to biobanking principles and topics, test played among the game developers and biobanking community at the German national biobanking symposium in Berlin, and further optimized. The main aspect here was design of the biobanking items with regard to a clear and unambiguous recognition of the distinct relevant biobank topics. Afterwards the decision on the production company was made by comparing four offers and the design was finalized. Initially 100 games were produced and distributed to the German biobanking community at production cost price.

The biobank game is a practical addition to the existing German Biobank Node online course "Biobanks - Theory and Fundamentals", which has already been succesfully integrated into three master´s programs in Leipzig, Göttingen, and Hannover.
The first evaluations of the use of the board game as part of university courses for students with and without the online course on biobanking were positive.

24: The Swedish Childhood Tumor Biobank- A national omics and tissue research resource for pediatric cancers

Assoc. Prof Teresita Díaz de Ståhl[1,2], PhD Gabriela Prochazka[1], Elisa Basmaci[1], Praveen Raj Somarajan[1], PhD Katarzyna Zielinska-Chomej[1], PhD Jenny von Salomé[1], MD, PhD Christopher Illies[1,2], MD, Prof Gustaf Ljungman[3,4], Johanna Sandgren[1,2]
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background
In Sweden approximately 350 children are diagnosed with cancer each year. Today more than 85% of the patients will survive, even so, cancer is one of the major medical causes of childhood death. Moreover, the survivors often suffer from sequelae due to the treatment. Therefore, deeper biological knowledge regarding these malignancies is essential for improved survival and quality of life for affected children. The aim of the Swedish Childhood Tumor Biobank (Barntumörbanken, BTB) is to increase the understanding of pediatric solid tumors by providing infrastructure resources, biological samples and molecular genetic/genomic data for research.

Methods
BTB has a multidisciplinary nation-wide collaboration with the six university hospitals that treat pediatric cancer patients. Fresh frozen tumors and blood samples are collected, and some additional sample types including parental blood and CSF. Also digital pathology slides are collected. BTB registers, prepares and stores the biobank samples with linked patient information, as well as performs whole genome sequencing (WGS), whole transcriptome sequencing (WTS) and methylation array (MA) profiling. BTB develops bioinformatic pipelines, together with the Science for Life Laboratory, internal variant databases and data portal structure for secure traceability, data/metadata organization and visualization.

Results
More than 2200 cases are now registered in BTB and 30 000 samples collected. Almost 1200 cases have been genomically characterized where BTB manages the generated data, including for the “GMS Barncancer” study where BTB is co-coordinating a national clinical implementation project for WGS and WTS analysis in the routine pediatric cancer care. BTB samples and generated data have so far been shared to >15 different research projects after formal application processes for secondary use. BTB is moreover assisting several clinical studies with sample logistics, regulatory support and data analysis/interpretation.

Discussion/Conclusions
BTB is a research infrastructure that systematically collects biological specimens and informed consent from more than 90% of the Swedish pediatric patients with solid tumors, and produce and manage high quality data. The continuous usage of the samples and the omics data in approved research projects will contribute to increased knowledge and likely have a positive impact on the future clinical care of children with cancer.

25: Development of a Convolutional Neural Network for Automated Copy Number Variants Validation and its Application in the UKB

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Neuropsychiatric disorders and Alzheimer's Disease, Cosmos 1-2, september 10, 2024, 15.30 - 17.00

Structural variants are a major source of variation in the human genome. In particular, copy number variants (CNVs) have been associated with multiple diseases and syndromes. CNVs are typically defined as deletions or duplications spanning ~50kbp to ~10Mbp.
Genotyping arrays still remain the most widely used platform to detect CNVs from, especially in large biobanks. However, CNV calling algorithms are prone to produce a high number of false positives (from 10% up to more than 50% depending on the level of sample quality), thus requiring analysts to manually "validate" calls. This has largely limited CNV research to the so-called recurrent loci.
We have developed a machine learning algorithm based on the convolutional neural network architecture that is capable of automating the visual validation of CNVs across the whole human genome. It was trained on ~15,000 human-validated examples from UKB singletons and Icelandic trios at deCODE genetics and has an accuracy above 90% across multiple cohorts and chip types, making it on average as good as a human analyst.
We showcase the application of this tool in the UKB, creating the first genome-wide map of validated CNVs in a large biobank population. Furthermore, we describe how CNVs are distributed across the genome and how regions are differentially permissive or intolerant to the presence of CNVs. Finally we show how to group CNVs making them akin to SNPs in association analysis and we present the results of the association of genome wide CNVs to a wide selection of phenotypes.

26: Mapping of HLA-DQ haplotypes in adults with coeliac disease in a large, screened population – results from the Norwegian HUNT study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction
The HLA-DQ2.5, -DQ2.2 or -DQ8 haplotypes are necessary for coeliac disease development with homozygotes of DQ2.5 carrying the highest disease risk. However, with only 1:4-1:7 of true patients usually diagnosed, the true haplotype distribution is unknown. We hypothesized that the distribution differs between known and new, previously undiagnosed patients.

Methods
A population-based study of 52,588 adults was screened for coeliac disease by serology, identifying 470 new cases (Marsh 3) in addition to 376 known cases identified via registries. All cases and a random sample of 1412 controls underwent HLA-DQA1- and HLA-DQB1-sequencing to infer relevant HLA-DQ haplotype combinations (DQ2.5/DQ2.5, DQ2.5/DQ2.2, DQ2.2/DQ7.5 [DQ2.5trans], DQ8/DQ8, DQ2.5/DQ8, DQ2.5/DQ7.5, DQ2.5/DQX, DQ2.2/DQ2.2, DQ2.2/DQ8, DQ2.2/DQX, DQ8/DQX, DQX/DQX [neither DQ2 nor DQ8]). Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results
Haplotype frequencies in cases vs. controls were 85.2% vs. 22.3% (DQ2.5cis), 8.3% vs. 21.6% (DQ8), and 1.2% vs. 8.2% (DQ2.2). DQ2.5 homozygosity carried the highest risk: OR 16.6 (CI 9.6-31.1), while DQ2.5/DQX had an OR of 6.3 (5.2-7.7). DQ2.5trans, although rare, still conferred a high risk (OR 10.6, 3.8-30.8). DQ8 homozygosity also posed a high risk (OR 7.5, 3.9-14.2) while DQ8/DQX had an OR of 2.1 (1.4-3.0). ORs for DQ2.2/DQ2.2 and DQ2.2/DQX were 3.0 (0.4-13.0) and 0.7 (0.3-1.3), respectively. No clear risk differences were observed between new and known cases, however, none of the new cases carried DQX/DQX in contrast to 5.6% of the known cases.

Conclusions
We found a gene-dose effect linked to DQ2.5 and DQ8 in both known and new cases, with a surprisingly high proportion of DQ8 for a Nordic population. Conversely, the large proportion of DQX/DQX in known cases compared to the absence in new cases, suggests a high prevalence of historically misdiagnosed patients.

27: Sample Service Coordinators support national biobank research in Sweden

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

To meet demands and needs of the Swedish researcher community, the national biobank infrastructure in Sweden (Biobank Sweden) decided in 2018, together with the Universities and the University Hospital Regions, to fund implementation of Sample Service Coordinators (PSK).
The mission of the Sample Service Coordinators is to support researchers who aim to collect samples at several locations in Sweden within the same study and to work towards improved national harmonization of sample handling. Also, Sample Service Coordinators give advice and support researchers who want to use existing samples for research, thereby increasing the utilization of biobanked sample collections.
Sample Service Coordinators are placed in Umeå, Örebro, Uppsala, Stockholm, Göteborg, Linköping and Lund and are operating at the local biobank or at a university.
How we work:
Sample Service Coordinators have good knowledge about local conditions for sample handling at the different biobanks in Sweden and can thereby guide researchers in national studies. Requests regarding collection of samples from researchers are being compiled in a document which is shared within the PSK-group. The Sample Service Coordinators meet online every week to plan and discuss coming and ongoing national studies. Working groups are formed to develop supportive documents.
The number of new coordinated national sample collections increased from 41 in 2018–2019 to 64 in 2022–2023 indicating an increase in interest to use support from Sample Service Coordinators.
Our vision is that Sample Service Coordinators:

- are well-known by the research community in Sweden and thereby support medical research
- will support a higher number of national sample collections in the future
- will improve national harmonization further to facilitate collection and use of biobanked samples

28: Large scale plasma proteomic profiling to identify candidate biomarkers of post-stroke functional outcome

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction: Stroke results in an immense health, societal and economic burden. Globally, about one in four adults will suffer a stroke in their lifetime. Stroke is a leading cause of death and disability. There is a large inter-individual variation in stroke outcomes, and part of this variation remains unexplained by clinical factors alone. Protein studies may offer insight into the biological mechanisms involved in injury and repair responses to cerebral ischemia.

Objective: To investigate a broad range of plasma proteins in relation to functional outcome after ischemic stroke.

Methods: Plasma protein levels were measured using the Olink® Explore 3072 high-throughput platform in 200 cases with acute ischemic stroke from the Sahlgrenska Academy Study on Ischemic Stroke phase 2 (SAHLSIS2). For individual proteins, associations to unfavorable 3-month functional outcome (defined as modified Rankin Scale score >2) were estimated by logistic regression. Machine learning methods, i.e. LASSO regression and Random Forest, were used to identify proteins and clinical variables with independent effects.

Results: The median age was 71 years, 61% were males, and 76 cases had unfavorable outcome. In total, 2254 proteins showed a prespecified call rate >80% and were included. In univariable single protein analyses, 172 proteins were significantly associated with outcome (FDR <0.05). Both machine learning methods selected the same five independent protein clusters as the variables that contributed the most to the separation of the unfavorable and favorable outcome groups. The five top proteins included neurofilament light chain (NfL, in validation of previous studies), and proteins involved in triglyceride metabolism, transcriptional regulation, neutrophil chemotaxis, and cytokine signaling. Also of note, including the two main clinical predictors of post-stroke outcome, i.e. age and stroke severity (NIH Stroke Scale score), in the machine learning models did not improve the discrimination between outcome groups compared to the selected proteins.

Conclusion: We identified multiple novel candidate plasma protein biomarkers of ischemic stroke outcome. Replication in other stroke cohorts as well as further investigations into the putative causal role of these proteins for ischemic stroke outcome are warranted.

29: Plasma Brain-Derived Tau is highly correlated to stroke infarct volume and improves outcome prediction in acute ischemic stroke

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Cardiometabolic Disorders II: Risk Predictors, Cosmos 1-2, september 11, 2024, 15.45 - 17.00

Introduction: Stroke is a leading cause of disability and death. Accurate prognostication is needed to guide patient care, target early rehabilitation efforts, select patients for clinical research, and convey realistic expectations to families. Ischemic stroke accounts for about 85% of all strokes, and there are currently no clinically available blood-based biomarker that accurately reflect neuronal injury in the acute phase of ischemic stroke. Such a biomarker could complement other clinical assessments in order to improve risk prediction.

Objective: To investigate whether the novel blood-based biomarker brain-derived tau (BD-tau) reflects neuronal injury in the acute phase of ischemic stroke and whether it can improve functional outcome prediction.

Methods: The present study included 713 ischemic stroke patients from the hospital-based observational, longitudinal cohort study SAHLSIS (Sahlgrenska Academy Study on Ischemic Stroke). Acute-phase plasma concentrations of BD-tau were analyzed using a novel ultrasensitive assay that selectively measures tau of central nervous system origin. Functional outcome 3 months after stroke onset was assessed using the modified Rankin Scale (mRS). Brain infarct volumes were calculated from magnetic resonance imaging (MRI) scans in a subset of 254 cases. Correlations between BD-tau and infarct volumes were evaluated by Spearman rank test. Associations between BD-tau and 3-month outcome were analyzed by logistic regression. The predictive performance of BD-tau was then tested over age and stroke severity as assessed by the widely used NIH Stroke Scale (NIHSS) using receiver operating characteristics curve (ROC) and area under the curve (AUC) analyses. The procedures were repeated stratified by infarct location according to the vascular territory (anterior versus posterior circulation) and anatomical location (right or left hemisphere versus brainstem or cerebellum).

Results: Plasma BD-tau concentrations and infarct volumes were highly correlated (rho 0.72, p 9x10-42). Correlations were of similar magnitude across all infarct locations. Among the 713 ischemic stroke cases (age 61 [53-67] years, 65% males) 185 had an unfavorable outcome (mRS score >2). Higher BD-tau concentrations were significantly associated with increased odds of unfavorable outcome after adjustment for age and NIHSS score (odds ratio per doubling of BD-tau: 2.0 [95% CI 1.7-2.5], p 8x10-12). BD-tau improved the prognostic accuracy significantly over age and NIHSS score (AUC for age + NIHSS 0.85 [95% CI 0.82-0.89] versus + BD-tau 0.87 [0.84-0.90]; DeLong p 0.02). In stratified analyses, the improvement by BD-tau was higher for infarcts in the posterior compared to anterior circulation. The greatest improvement in prognostic accuracy was for infarcts in the brainstem or cerebellum (AUC for age + NIHSS 0.74 [0.58-0.89] versus + BD-tau 0.87 [0.78-0.96]; DeLong p 0.009).

Conclusion: These findings suggest that plasma BD-tau concentrations can provide valuable information on the extent of neuronal damage in acute ischemic stroke regardless of the infarct location. Furthermore, plasma BD-tau demonstrated utility as a biomarker to improve risk prediction for an unfavorable outcome, especially for infarcts in the posterior circulation. BD-tau is thus a promising, accessible, and minimally invasive neuronal injury biomarker and could have clinical use to complement the NIHSS score and other clinical examinations for acute ischemic stroke.

32: Parity modifies the effect of genetic variants associated with gestational duration

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Preterm delivery is the leading cause of death among children under five years of age. Still, the biological understanding of delivery mechanisms is poor, and maternal genetics may have an important role in expanding that knowledge. Parity is a well-known risk factor that has a large effect on gestational duration variance suggesting varying conditions between pregnancies and the presence of interactions.

In this study, we explore if parity modifies the maternal genetic effects on gestational duration (Gene x Parity interactions) using data from 55,486 mothers in The Norwegian Mother, Father, and Child Cohort Study. Potential genetic effect differences were investigated by performing parity stratified genome-wide association studies, assessing the genetic correlation of gestational duration by parity, testing for single SNP x parity interactions, and testing the interaction between a polygenic prediction of gestational duration and parity on gestational duration.

Our results indicate that parity modifies the maternal genetic effects on gestational duration, with a stronger genetic effect in a woman's first pregnancy. For instance, more variants reached the genome-wide significant level in a woman's first pregnancy compared to other pregnancies. Stratifying by parity, the polygenic prediction had a larger prediction accuracy on gestational duration in the first pregnancy compared to other pregnancies.

In conclusion, our study reveals that parity modifies the maternal genetic effects on gestational duration and highlights the relevance of considering parity in genetic studies of gestational duration.

33: Accessing Swedish biobank cohorts: practicalities and some legal aspects

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Implementing Biobank Standards, Cosmos 3AB, september 11, 2024, 15.45 - 17.00

Introduction: Swedish biobank cohorts are a gold mine for medical research, used in some 300-400 publications annually. The Swedish personal identity number facilitates the combination of samples and data with health registers and medical records, making it possible to study risk factors before a disease became apparent. This is, however, only possible if certain administrative and legal hurdles are overcome. We aim to present key steps required to access these resources, as well as some legal aspects that may stand in the way.

Methods: We are currently interviewing Swedish biobank cohorts in order to map out the process and obstacles in accessing data and/or samples.

Results: The findings so far show that the main steps and issues are similar:

1. Finding the cohort: Researchers find the cohorts through colleagues or scientific publications. Visibility in catalogues is not as fruitful, yet. Most cohorts have a website explaining what resources are available, the application process, and whom to contact.
2. Applying for sample and/or data access: Typically, an access committee assesses the scientific value of the study and ensures that resources are used well e.g. by minimizing study overlap and, if applicable, sample volumes. Most cohorts have an application fee as well as fees for data and sample retrieval.
3. Ethical review: Research projects require Swedish ethical approval for any part of the research carried out in Sweden. Applications to the Swedish Ethical Review Authority need to be written in Swedish. Research projects based outside of Sweden therefore typically require collaboration with a Swedish research institute. Some cohorts have a broad ethical approval that can cover certain research projects.
4. Data access: Cohort baseline data is generally easy to access, but linkage to national registries is often a slow process. A newly proposed national legislation for certain research databases could improve data access by allowing cohorts to hold national registry data themselves. Data sharing with countries outside the EU/EES is yet another bottleneck that in some cases cannot be overcome.
5. Sample access: Time for sample retrieval varies largely from a few months to around one year, due to constraints in personnel in the laboratory or administration. The Swedish Biobank Act requires that Material Transfer Agreements (MTAs) are signed before samples are sent for analyses. Cohorts may request that new data is returned to the cohort. Some cohorts are moving towards becoming a provider of data rather than samples, following extensive sample analyses. Sustainability issues of long-term freezer storage is an increasing concern.
6. Publication: Cohorts may suggest collaboration with a researcher that has certain knowledge regarding the cohort. Most cohorts request acknowledgement in publications.

Discussion: Biobank cohorts in Sweden, and presumably other countries too, are battling issues such as procuring long-term funding for freezer storage, increased complexity regarding legal aspects, and the need to ensure their continued use in research projects. How can we keep these resources alive? Suggested changes to national legislation might help to some extent. Could the European Health Data Space be a saviour in part?

34: Predicting first-episode psychosis using polygenic risk and longitudinal child and adolescent phenotypes

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Late adolescence and early adulthood are sensitive periods for the development of psychotic disorders. Psychosis first typically appears in early adulthood, but prodromal symptoms can emerge during adolescence, and developmental soft signs may appear in childhood. However, many individuals experiencing first-episode psychosis typically wait years for a diagnosis. Thus, identifying those at risk of transitioning to psychosis is essential. Our goal is to create a combined predictive model in a broadly defined high-risk group using genetic risk scores, prodromal symptoms, and childhood soft signs to predict conversion to psychosis. Genetic and diagnostic registry data were collected from children (total n ~114,000) in the Norwegian Mother, Father, and Child Cohort Study (MoBa). Our high-risk groups were defined by familial risk, prodromal symptoms, or genetic liability (n ~4,000). Children from MoBa have been followed from gestation (mothers included between 1999-2008) and into their teens. We will use information on development and mental health collected at six and 18 months and three, five, eight, and 14 years and calculate polygenic risk scores (PRS) for schizophrenia (SZ). We then apply a machine learning algorithm (RUSBoost) using SZ PRS and selected diagnostic, developmental, and mental health variables to predict conversion. We will lastly perform feature selection, comparing the various predictors. At the BGA annual meeting, we will present our results and discuss possibilities to improve these models. Hopefully, this project can pave the way for improved prediction models of high-risk individuals for improved early intervention and support.

35: Parent of origin effects in psychiatric disorders

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Parent of origin effects are genetic effects on a phenotype that depends on the parent from which alleles are inherited. Parent of origin effects are generally understood to have an epigenetic basis mediated by processes such as differential methylation, and have been shown to be associated with some complex phenotypes. However, we still lack an understanding of many parent of origin effects, in large part because they are difficult to study at scale. Allelic parent of origin is not observed in an individual genetic data and must be inferred, often by genotyping and phasing trios. This requires genetic data from an offspring and both parents, severely limiting the scale of studies investigating parent of origin effects. Recent methodological advances have opened up the study of parent of origin effects in biobanks where there is no information about the parents' genotypes, but these methods do not incorporate pedigree information and can generally only infer allelic parent of origin in males.

Here we conduct one of the parent of origin largest associations studies to date by combining three distinct data sources: 1) genetic data from iPSYCH 2012 and 2015i cohorts, 2) family relationship data from the Danish civil registry, and 3) phenotype information from Danish health registers. In our novel method, we use the population pedigree described in the civil register to assign the parent of origin within identical-by-descent (IBD) segments shared by distant relatives. This leverages the extensive birth registry to provide additional information on how the genotyped samples from iPSYCH are related. This increases the number of samples where parent of origin inference is possible vs when pedigree information is not incorporated. We then expand the parent of origin inference within each sample to the whole genome via phasing and imputation.

Across both iPSYCH studies (n=134,230), we are able to establish the parent of origin with high confidence in approx. 80% of the genome for n=37,045 samples, representing one of the largest parent-of-origin data sets to date. We will conduct parent of origin genome wide association studies (GWAS) to investigate associations between allelic parent of origin and psychiatric phenotypes including schizophrenia, autism, attention-deficit/hyperactivity disorder, affective disorder, in addition to other phenotypes.

36: Successful decade of LOY and other examples of mosaicism in normal tissues preconditioning for cancer

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Post-zygotic mutations in normal cells and tissues are increasingly recognized as frequent and important in disease predisposition. However, existing biobanks are rarely collecting normal tissues that could be used in research of disease predisposing post-zygotic mutations.

We therefore established a dedicated biobank allowing for comprehensive analyses of these mutations that may predispose to breast-, prostate-, colon-, bladder-, kidney- and pancreas cancer. Selected examples of post-zygotic mutations from projects focusing on breast-, prostate-, and bladder cancer will be presented.

For breast cancer study, the analysis of non-cancerous mammary gland tissues from cancer patients show widespread variation on the level of structural genetic variants (deletions, gains and copy-neutral loss of heterozygosity), point mutations and altered transcriptional profiles. A distinct gene expression signature was identified in normal samples, featuring key cellular components encoding keratins, CDH1, CDH3, EPCAM cell adhesion proteins, matrix metallopeptidases, oncogenes, tumor suppressors and others (FOXA1, RAB25, NRG1, SPDEF, TRIM29, and GABRP). This signature, named KAOS (for Keratin-Adhesion-Oncogenes-Suppressors) was associated with increased mortality rates.

For the bladder cancer project, we analysed 277 samples of histologically normal urothelium, 145 tumors and 63 blood samples from 52 males and 15 females, using the in-house adapted Mosaic Chromosomal Alterations (MoChA) pipeline. Overall, 45% of patients exhibited at least one alteration in at least one normal urothelium sample. Recurrence analysis resulted in 16 hotspots composed of either gains and copy number neutral loss of heterozygosity (CN-LOH) or
deletions and CN-LOH, encompassing well-known and new BLCA cancer driver genes. We provide a proof of principle that our approach can characterize the earliest alterations preconditioning normal urothelium to cancer development.

Acquired during life loss of chromosome Y (LOY) is the most common post-zygotic mutation and a successful decade of research suggests its importance in shaping the immune system's activity. Multiple discoveries in this new field revealed the impact of LOY on many chronic diseases; e.g. cancer, neurodegeneration, cardiovascular outcomes, and acute infections. LOY is a highly dynamic mutation with pleiotropic effects.

Our recent research revealed that regulatory T-lymphocytes (Tregs) in tumor microenvironment (TME) of primary colorectal cancers and liver metastases had the highest frequency of LOY (22%) in comparison to CD4+ T-lymphocytes and cytotoxic CD8+ T-lymphocytes. LOY scored in scRNA-seq was also linked to higher expression of PDCD1, TIGIT and IKZF2 in Tregs. PDCD1 and TIGIT encode immune checkpoint receptors involved in the regulation of Tregs function. This sets the direction for further research regarding a probable role of LOY in intensifying features related to the suppressive phenotype of Tregs in TME and consequently a possible influence on immunotherapy response in colorectal cancer patients.

37: Identifying proteins that mediate the association between hormonal contraceptive use and breast cancer development: A two-stage observational and Mendelian Randomization study

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Precision Cancer Medicine, Cosmos 1-2, september 12, 2024, 11.00 - 12.00

Background
It is known that hormonal contraceptives (HC) increase the risk of breast cancer. However, the underlying mechanisms are inconclusive. To fill this knowledge gap, we here employed a two-stage study design to identify proteins that are potential mediators of the effect of HC use on breast cancer risk using proteomics data for around 3000 plasma proteins.

Method
First, we estimated the effect of progestogens-only HCs (either oral progestogens or intrauterine devices) and oral combined HCs (estrogen and progestogen combined) on the level of 2923 plasma proteins in 5,242 pre-menopause women in the UK Biobank (age: mean ± SD 44.8 ± 2.7 years) applying linear regression. Among them, 186 women were current users of combined HCs, 360 women were current users of progestogens-only (n = 260 users of oral progestogen and n = 100 IUD users) and 4,596 women were non-users. Analyses were adjusted for age, age-squared, body mass index (BMI), waist-to-hip ratio and smoking. In the second stage, we performed a series of two-sample inverse-variance weighted (IVW) Mendelian Randomization (MR) analyses for significant proteins from the first stage (after correction for multiple testing) to identify the proteins with possible causal effect on breast cancer that potentially mediate the effect of HC on development of breast cancer. The genetic instruments for the selected proteins, were identified from a previous GWAS study identifying pQTLs for the 3000 proteins in UK Biobank. To be able to evaluate pleiotropy in the MR, we included only proteins with at least three independent pQTLs, of which at least one was cis-regulatory. The effect of the genetic instruments on breast cancer was estimated using data from a previous meta-analysis comprising 82 studies from the Breast Cancer Association Consortium (BCAC) and 60 studies from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA).

Results
We identified 56 proteins associated with using progestogens-only medications and 621 proteins associated with taking combined HC. Out of 56 proteins associated with progestogens-only HC, we performed the two-sample MR for 50 proteins. Only one protein, Carboxypeptidase M (CPM), showed significant causal association with breast cancer after Bonferroni correction. Regarding oral combined contraceptives, 574 proteins were used for MR analysis of which, 6 proteins were significantly associated with breast cancer (after correction for multiple testing). Receptor-type tyrosine-protein phosphatase mu (PTPRM), had the strongest association (P-value 2.36x10-10, odds ratio 0.90, 95% confidence interval 0.87 to 0.93). In vitro knockdown cell experiments have revealed a correlation between reduced expression of this protein in breast cancer and poor prognosis, as well as diminished disease-free survival of patients. The other five significant proteins include ICAM5, EPHA4, OMG, ENG and CST6.

Conclusions
Our results suggest that the effect of HC use on development of breast cancer is partly mediated through the expression of different proteins. Identifying these proteins and their direction of effect could reveal potential new intervention targets against breast cancer development and eventually may assist us in mitigating the effects of HC use on the development of breast cancer.

38: Machine Learning for Genetic Studies - Exploring the Potential of Machine Learning Models forPredicting Preterm Delivery using Genetic Markers

Hedvig Helena Sundelin[1], Phd Julius Juodakis[1], Prof Bo Jacobsson[1,2], Phd Pol Sole-Navais[1], Ms Karin Ytterberg[1]
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Preterm delivery (PTD) is a significant contributor to infant mortality and morbidity worldwide, influenced by environmental and genetic factors. Although previous studies have identified genetic variants associated with PTD and gestational duration, their effect sizes remain relatively small, leaving a substantial portion of the hereditary variation unexplained. This thesis explores the potential of machine learning (ML) techniques to uncover additional insights into PTD and gestational duration using genetic data.

The background section underscores the global impact of preterm birth on child mortality and long-term health outcomes, emphasising the role of genetics with an estimated heritability of around 30%. This project aims to apply ML techniques to improve the prediction of gestational duration and PTD based on genetic data. Research questions address ML model selection, the impact of variables on prediction performance, and a comparison to previous studies. The study is based on the Norwegian Mother, Father and Child Cohort Study (MoBa) and uses data from the Medical Birth Registry of Norway (MBRN). The scope includes the use of genetic data and a focus on the 23 loci previously identified in a related study. The theory chapter provides an overview of genetics and its application in studying complex conditions like preterm delivery. It also introduces ML and explains the theoretical foundations of different ML models. Subsequently, the methods and materials chapter describes the data acquisition process, preprocessing steps, employed ML classifiers, and model evaluation methods. The chapter highlights the use of neural networks, classic ML algorithms, and libraries for implementation. Results reveal varying AUC scores among classic models, with logistic regression (LR) performing the best. The choice of variables had a significant impact, with the maternal genome and the Top 23 set, offering the best conditions. Network models achieved comparative scores for binary classification. Additional analyses on the predicted probabilities demonstrated higher AUC scores compared to binary classifications, identifying RMSprop as the best-performing network model. The study reveals a slight improvement in results compared to Polygenic Risk Scores (PRS) but a modest predictive ability overall. The findings in this study suggest that more extensive research is needed to unveil the potential of ML models in improving predictions based on genetic data.

39: GLP-1 receptor agonist treatment in early pregnancy and risk of pregnancy complications - A nationwide cohort study

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Precision perinatal and newborn medicine, Cosmos 1-2, september 11, 2024, 11.00 - 12.00

Study question:
Does periconceptionally exposure to GLP-1 receptor agonist (GLP-1 RA) treatment increase the risk of pregnancy complications?

Background:
The prevalence of obesity continues to increase globally, affecting half the adult population in Western countries, increasing the risk of infertility and obstetric and neonatal complications. Weight loss might improve risks, leading to an interest in effective weight loss methods such as GLP-1 RAs. However, none of the GLP-1 RAs are approved for use during pregnancy and at least two months before to avoid fetal toxicity. The current recommendations are based on a fetal safety principle and data from animal studies, clearly underscoring the need for more human evidence about the effect of GLP-1 RA use in the periconceptional period.

Study design:
A Danish nationwide observational cohort study of 522,209 pregnancies from October 2009 until June 2019 with data from health and socioeconomic registries at Statistics Denmark: National Prescription Register, National Patient Register, Medical Birth Register, Educational Register and Central Persons Register. All registries had complete information until June 2019, except the National Prescription Register which was until December 2018. The unique personal identification number used in Denmark enables direct linkage of individual-level information across registries.

Methods:
Exposure was defined as the redemption of a GLP-1 RA prescription, liraglutide, +/-eight weeks from last menstruation. Primary outcome: any complication (pre-eclampsia, gestational diabetes (GDM), preterm birth (<37+0), low birth weight (<2500g), small-for-gestational-age, or large-for-gestational-age (LGA)). Evaluated risk of individual outcomes, and effect on gestational age, birth weight, and placenta weight. Outcomes were compared to an unexposed control group, weighted using fast generalized matching based on propensity score estimated from relevant confounders. Risk ratio and 95% confidence interval (CI).

Main results:
Within the study population of 522,209 pregnant women, we identified 93 exposed to liraglutide in early pregnancy. Exposed women were on average older, had a higher BMI (~40% higher), and had a sixty times higher frequency of diabetes (DM1 or DM2) compared to unexposed women giving birth in the same period ($p < 0.001$). Liraglutide exposure was associated with a higher risk of obstetrical complications, pre-eclampsia, GDM, and preterm birth. No difference in the birth weight, but those exposed were more likely to give birth to an LGA child ($p < 0.01$). However, we did not find any evidence of increased risk when utilizing a propensity score matching method ($p > 0.1$). This indicates that liraglutide, in itself, is not driving the increased risk, but the indication for a GLP-1 RA prescription (e.g. diabetes or obesity) is the causal factor. The finding did not depend on the choice of method for propensity score matching.

Findings pertaining to liraglutide and semaglutide, encompassing the period from 2009 to 2023, will be showcased at the primary conference.

Wider implications:
The study is important for counseling women periconceptionally exposed to GLP-1 RA, that there is no evidence of an increased risk of pregnancy complications. It calls for studies on the safety profile for GLP-1 RA treatment in women, enabling early weight management for the benefit of the mother and child.

41: Dissecting body mass index as a risk factor for myocardial infarction: insights from a multivariable mendelian randomisation study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Objectives:
Myocardial infarction (MI) remains a major cause of death worldwide despite use of statin therapy. Often asymptomatic, MI can lead to adverse clinical events or sudden death. Genetic predisposition and lifelong exposure to atherogenic conditions contribute to its development. While obesity rates have surged in recent decades, the incidence of MI presents an intriguing contrast. Could preventive treatments (such as lipid-lowering and antihypertensive drugs) be influencing this apparent discrepancy? Obesity is linked to elevated blood pressure and unfavourable lipid profiles, but it remains uncertain whether the association with MI is solely mediated through these factors. To explore this, we conducted a multivariable Mendelian Randomization (MR) study and mediation analyses using body max index (BMI), low-density lipoprotein (LDL), triglyceride levels (TG), and systolic blood pressure (SBP). Our objective is to unravel the intricate relationship between obesity and MI risk.

Methods:
We extracted independent genetic instruments from the UK Biobank by filtering for common and significant SNPs (p-value <= 5e-08; minor allele frequencies <= 0.01) for the following exposures: BMI (442 SNPs), LDL (39 SNPs), SBP (263 SNPs) and TG (297 SNPs). These SNPs were then matched with those present in MI dataset from the CARDIoGRAMplusC4D consortium (cases = 43,676; controls = 128,199). F-statistic and conditional F-statistic were calculated to check the absence of weak instruments. We performed both univariable and multivariable MR analyses to estimate causal effects, followed by several sensitivity analyses, to ensure the validity of the causal inference. Our methods included inverse variance-weighted, Egger, simple and weighted-median, MR-PRESSO and Lasso. Due to considerable heterogeneity, we report the statistical estimates obtained using the Lasso method. Sobel's tests were used to assess the presence of a mediation effect.

Results:
From univariable analyses, the causal effects of BMI, LDL TG, and SBP on MI were found to be significant. In the multivariable framework, we explored the potential mediating effect of BMI through SBP, LDL, and TG. When adjusting for SBP, the effect of BMI on MI was reduced (OR_univariable = 1.53; 95%CI: 1.44-1.62; p-value = 3.11e-45; OR_multivariable = 1.39; 95%CI: 1.30-1.49; p-value = 3.61e-24). BMI also showed a reduction in effect (OR_multivariable = 1.39; 95%CI: 1.30-1.48; p-value = 8.44e-24), when adjusting for TG. However, when adjusting for LDL, the direct effect of BMI (OR_multivariable = 1.56; 95%CI: 1.46-1.66; p-value = 7.40-45) was close to the corresponding total effect (OR_univariable = 1.53). Sobel tests indicated that a significant fraction of the total effect of BMI on MI is mediated through SBP (p-value = 1.81e-6), as well as through TG (p-value = 5.94e-5), but not through LDL. The proportion of mediated effects through both SBP and TG were estimated to 40%.

Conclusion:
This study supports the presence of a mediation effect of SBP and TG in the causal relationship between BMI and MI. By identifying potential mediating factors, future research should continue to elucidate the complex mechanisms behind the observed effect of obesity on MI. Ultimately, such findings may inform targeted preventive strategies, deepening our understanding of cardiovascular diseases amid rising obesity rates.

Next pregnancy after Pregnancy Loss – Copenhagen Pregnancy Loss (COPL) cohort.

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Biobanks, Research, Innovation, Precision Medicine as a foundation of future health, Cosmos 1-2, september 10, 2024, 13.20 - 15.10

Background: 25% of all pregnancies end with a pregnancy loss (PL). Half of the PLs are caused by aneuploidi (abnormal number of chromosomes), but almost 50 % of all PLs remain unexplained.
In November 2020, the enrollment for Copenhagen Pregnancy Loss (COPL) project started, with the aim of identifying causes, risk factors and treatments for PLs. 3000 women/couples experiencing a PL will be included in the COPL project. Biological samples, including blood samples, urine samples and rectal swap from included women and men, vaginal swap and fetal tissue from the women, and semen sample from the men, are collected at the day of the PL. Further blood samples, urine samples and vaginal swap are collected from the women 8 weeks after the loss. Chromosome analyses of the fetus' are made from cell-free fetal DNA on the women's blood (Schlaikjær Hartwig T, et al., Lancet, 2023; PMID: 36739882) and the results are given to the couples during a follow-up visit 8 weeks after the PL. Other samples are biobanked for further analyses, including full genome sequencing and analyses using omics technologies, among others.
Studies have shown that there is an increased risk of experiencing a new PL if previous loss was euploid (normal number of chromosomes) (Ogasawara M, et al., Fertil Steril, 2000; PMID: 10685533). However, there is still limited knowledge about different causes for the euploid losses. The hypotheses are, that underlying maternal conditions might be causal, but it remains to be elucidated. Thus, there is still an unmet need for identifying causal factors important to predict pregnancy outcomes in the next pregnancy after a PL.

Aim: To find potential markers for pregnancy outcomes in women after experiencing a PL, and further understand the mechanisms in early-stage pregnancies.

Method: 1000 women with their first pregnancy after included in the COPL cohort, will be enrolled and establish a cohort with longitudinal sampling during pregnancy. All included women have at least one previous PL in the COPL project. On the day of a new positive pregnancy test (gestational age 4-5 weeks), the women will have blood samples drawn. Afterwards, blood samples will be drawn, and transvaginal ultrasound will be performed continuously every second week during the first trimester, and one time during 2nd and 3rd trimester (figure 1). At the day of delivery, blood samples will be drawn from the mother and from the umbilical cord. During all visits, the women will answer questions regarding pregnancy symptoms, bleeding, and medication during the pregnancy. All blood samples will be biobanked for further analyses using omics technologies. If the women experience a new PL, they will be offered to be enrolled in the COPL project again with non-invasive prenatal testing for phenotyping the lost fetus.

Perspectives: Establishing a cohort with longitudinal sampling from PL, pre-pregnancy and during pregnancy entails a unique opportunity to investigate early-stage pregnancy, and potential markers for pregnancy outcomes, with inter-and intra-individual variations, and with the ultimate aim of improving maternal health and fetal survival.

43: EPITOP Biobank: Innovative collection of residual clinical blood volumes from extremely preterm infants for biomarker research

Ulrika Sjöbom, PhD Ruth Wickelgren[3], Jenny Isaksson[4], Ass. prof Anders K. Nilsson[2], Tove Hellqvist[2], MD, PhD Karin Sävman[5,6], Prof. Ann Hellström[2], Ass. prof Chatarina Löfqvist[1,2]
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Selected Biobank Abstracts, Cosmos 3AB, september 12, 2024, 11.00 - 12.00

Background: Despite advancements in neonatal medicine, extremely preterm infants (<28 weeks gestation) continue to experience high morbidity and mortality rates. Blood-based biomarkers hold promise for early detection, risk prediction, and treatment, ultimately improving clinical outcomes for this vulnerable population. However, ethical concerns surrounding the collection of additional research samples from these infants, including informed consent, parental anxiety, and potential harm, must be addressed. The EPITOP neonatal biobank aims to collect residual blood volumes from routine analyses. It addresses ethical challenges with a robust framework, ensuring responsible sample and data management while safeguarding infant and family rights.

Method: Approved by the Ethics Review Authority in June 2019 (dnr 2019-03110 and 2019-02321), the EPITOP neonatal biobank collaborates with the Neonatal Intensive Care Unit (NICU), the Department of Laboratory Medicine, and the Regional Biobank Center at Sahlgrenska University Hospital, Göteborg, Sweden. Following written parental consent, residual volumes are collected from clinical samples from infants born at <28 weeks gestational age admitted to the NICU. The first collection started in 2020 and is set to be finalized in December 2024. A database on the infants will be constructed based on information from medical charts, and Swedish Neonatal Quality Registers (SNQ).

Results: As of 1st of March 2024, 215 infants were eligible for EPITOP collection, with 121 informed consents obtained. The mean gestational age in the cohort is 25.4 (SD 1.38) weeks (range 22 +3 – 27 + 6 weeks + days) from 56 (45.9%) girls. For 70 of the 94 infants who were not included, appropriate staff could not inform and include them in the study, with the main reasons being early death, language difficulties, or early transportation to another hospital, and 24 (11%) cases declined study participation. In total, 4238 samples were collected from residual clinical volumes after blood gas (>90% of the samples) and haematology analyses. The highest frequency of sample collection was within the first week or weeks after birth. Feasibility projects have been conducted to assess the quality and useability of the samples, evaluating the stability of CD34+ stem cells, fetal haemoglobin, and sex steroids. The first sets of samples have been selected for ongoing longitudinal biomarker studies, enabling a high resolution of samples and sufficient residual volumes.

Conclusion: With its salvaged longitudinal blood samples, the EPITOP neonatal biobank can provide a valuable resource for discovering and validating novel biomarkers in preterm infants without exposing these vulnerable infants to iatrogenic phlebotomy for research purposes. Ongoing studies using these biomarkers may significantly advance the precision and effectiveness of treatments for these at-risk infants.

44: The Northern Sweden Health and Disease Study (NSHDS): An update after almost 40 years of sample collection and research

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction
The Northern Sweden Health and Disease Study (NSHDS) is based on three sub-cohorts: the Västerbotten Intervention Programme (VIP), the Northern Sweden Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA), and the Mammography Screening Project (MSP). VIP is both a community-based intervention programme encouraging healthy lifestyle (targeting individuals 40, 50, and 60 years of age), and a corresponding research cohort. MONICA is based on a series of cross-sectional surveys recruiting at 25-74 years of age. MSP recruited women attending mammography 1995-2006. Data on health and lifestyle, anthropometric measures, blood pressure, blood lipids, and glucose tolerance are available for most participants. Blood samples were fractioned, frozen within one hour of collection, and stored at -80 °C. The first complete sample (plasma, buffy coat, and erythrocytes) in NSHDS is dated October 1, 1986. It is a VIP sample. Recruitment and sampling is still ongoing.

Aim
To provide an update on NSHDS

Results
Participants: The cohort now consists of >140.000 participants in the two northernmost counties in Sweden (Norrbotten and Västerbotten). They have provided blood samples at >240.000 occasions with 1.5 million person-years of follow-up.

Scientific result: More than one thousand publications and >60 PhD theses have used NSHDS. Findings include evidence for associations of viruses with subsequent disease risk, including Epstein-Barr virus with multiple sclerosis, herpes simplex virus with Alzheimer's disease, and human papillomavirus with cervical cancer. Other findings include associations between altered protein levels and aortic stenosis risk, and between high sugar intake and increased total mortality. More recent studies advanced the understanding of biomarker-disease association in e.g. type 2 diabetes, cardiovascular disease, spondyloarthritis, and B cell lymphoma. NSHDS has also contributed to several large international efforts, such as the development of risk prediction models for primary prevention of cardiovascular disease and early lung cancer detection.

Challenges: In parallel with the research activities, NSHDS has faced several challenges through the years, often related to organization, main direction, or sustainability. Todays' main challenges seem to relate to: A) increased regulation regarding data protection, resulting in administrative and legal restrictions, and B) a shift in researchers' interest from analysing samples to accessing data from already performed chemical analyses. B might partly be a result of A.

Current developments: One focus right now is to adapt to a suggested new legislation, 'Act for certain research databases', which could potentially help us overcome some of the administrative and legal hurdles that cohorts currently face in Sweden. Another focus is on the project Personalised screening, risk prediction, and understanding disease trajectories for early detection of disease – An integrated cohort approach (PREDICT). PREDICT creates a case-cohort dataset with >50.000

individuals, including cases of various diseases and a subcohort of 7.500 individuals. Samples will be analysed for a range of biomarkers, and a new database will be constructed.

45: Understanding sleep and metabolic traits in ME/CFS

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a poorly-understood disease that affects an estimated 17-24 million individuals worldwide. Often preceded by an infection, the symptoms manifest as debilitating fatigue that in severe cases requires near-constant isolation in a dim, quiet room. Earlier reports show that circulating metabolites and particularly glucose are affected in ME/CFS. In chronic viral infection, hypothesized to be a cause of ME/CFS in at least a subset of patients, high levels of the cytokine interferon gamma leads to isolated insulin resistance in skeletal muscle. This local insulin resistance leads to a compensatory increase in insulin production in the liver, reducing glucose production via gluconeogenesis and resulting in transient peripheral hypoglycemia.

To investigate the role of sleep and altered glucose metabolism in ME/CFS, we obtained genome-wide association study (GWAS) summary statistics for sleep traits from the UK Biobank and fasting glucose, fasting insulin and other glucose metabolism traits from the MAGIC consortium. We additionally obtained body mass index (BMI) GWAS summary statistics from the GIANT consortium. We compared these summary statistics to a genome-wide association study meta-analysis of ME/CFS performed on individuals from the national FinnGen study, the UK Biobank, the Estonian Biobank, and the Mass General Brigham Biobank (N = 3908 cases with ME/CFS and over one million disease free controls). We performed genetic correlation with LD Score Regression (LDSC) between ME/CFS and metabolic traits, and two-sample mendelian randomization with significant single-nucleotide polymorphisms as exposures predicting ME/CFS as an outcome.

We found no significant genetic correlation between ME/CFS and glucose metabolism traits or BMI, suggesting that genetic variants associated with typical glucose metabolism were not related to those underlying liability to chronic fatigue syndrome. In contrast, ME/CFS correlated with long sleep duration and chronotype ($P < 0.05$). While glucose metabolism and ME/CFS are likely controlled by separate genetic risk factors, the findings indicate a connection between sleep and ME/CFS. We also found no significant causal relationship between genetic instruments associated with glucose metabolism and ME/CFS, indicating that altered glucose metabolism is likely not causal in the development of chronic fatigue.

Comprehensive cancer-oriented biobanking for post-zygotic genetic variation in cancer predisposition

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Biospeciment Science, Sample Handling and Quality, Cosmos 3AB, september 11, 2024, 14.00 - 15.15

One of the prerequisites for translational research is availability of well-characterized samples of different types from patients suffering from various diseases and control groups. Post-zygotic genetic mutations (PZM), also called somatic mutations, play a role in the origin of various diseases, such as cancer and neurological disorders. Unlike mutations inherited via germline, PZMs often act as early indicators of disease and can precede the onset of clinical symptoms by years. The primary goal of 3P-Medicine Laboratory is to investigate the role of PZMs in age-related diseases, emphasizing sporadic cancer and developing innovative strategies to improve diagnostics and prognosis. The rationale behind our biobanking approach is explorations of post-zygotic pathogenic gene variants, especially in non-tumoral tissue, which might predispose to cancers.

The diagnoses collected by us included carcinomas of the breast (mastectomy or breast conserving surgery), colorectal, prostate, kidney, urinary bladder (cystectomy or transurethral resection), exocrine pancreatic carcinomas as well as metastases of colorectal cancer to the liver. We also collected age-matched normal controls. The collection gathered from 2019 to 2023 originates from five hospitals and reached over 3500 patients and controls, yielding a total of over 45000 original samples and over 35000 derivatives of various types. The predominant diagnosis is breast carcinoma, with nearly 1400 donors, followed by colorectal carcinoma (870 donors), prostate carcinoma (505 donors), renal carcinoma (244 donors), bladder carcinoma (243 donors), exocrine pancreatic carcinoma (47 donors) and metachronous colorectal cancer metastases to liver (33 donors). Forty percent of the total sample count originates from macroscopically healthy cancer-neighboring tissue, while contribution from tumors is ~15%, which makes collection a unique source for cancer predisposition studies. Moreover, the collection of controls comprises 225 donors without the history of cancer. To facilitate biobanking procedures both at clinics and onsite, we developed two program packages, enabling registration of patients, clinical data and samples at the participating hospitals as well as the central system of sample/data management at coordinating center. The approach used by us may serve as a model for dispersed biobanking from multiple satellite hospitals. The scale of biobanking and the specificity of PZM studies required also development of unified sample collection protocols, using well-defined clinical criteria for patient inclusion. These protocols were developed in close collaboration between the molecular biologists, surgeons involved in patient recruitment and treatment and pathologists.

Our biobanking resource facilitated comprehensive projects in our unit and collaborators. It will further stimulate research into genetic mechanisms behind the development of common cancers by applying “-omics” approaches on DNA-, RNA-, protein- and tissue levels. It also demonstrated that possibility for integrated biobanking in Poland is feasible and its implementation relies more on funding and decision-making levels than organizational issues.

47: Host genome-wide association study of the Swedish gut microbiome

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Selected young researchers' talks 2, Cosmos 1-2, september 12, 2024, 14.30 - 15.00

Objective: An improved understanding of host genetic determinants of the gut microbiome may provide insights in physiological mechanisms. Here, we present results from the largest metagenomic sequencing-based genome-wide association studies (GWAS) of the human gut microbiome in 16,017 participants, aged 18-96, from the population-based Swedish studies of SCAPIS, SIMPLER and MOS.

Methods: After processing all metagenomes with the same pipeline and imputing the human genotypes against the HRC1.1 reference panel, a series of GWAS were conducted for 919 microbial species using REGENIE. We assessed presence/absence for species with 5-50% prevalence, and rank-inverse normalized relative abundance for species with prevalence ≥50%. Covariates were sex, age, age2, metagenomic DNA extraction plate and genetic principal components. Cohort-specific results were meta-analyzed using METAL.

Results: We identified 8 study-wide (p-value<5x10-8/919) and 98 genome-wide significant (p-value<5x10-8) loci associated with up to 11 microbial species. Besides the repeatedly replicated ABO and LCT loci, we identified at study-wide significance loci that have previously been reported at genome-wide significance such as FUT2, and novel loci associated with the gut microbiome, including a locus between genes FUT3 and FUT6. Results were consistent across cohorts.

Conclusions: The large sample size and harmonized data allowed for the discovery of new host genetic loci associated with human gut microbial species, including more blood group and secretor status loci. We plan to further replicate these findings and to share the complete GWAS summary statistics with the research community. Of note, we are currently performing GWAS for microbial alpha diversity, genes and function.

48: Quality and quantity of gDNA from blood cells in SST-clots stored for 8 to 18 years - The SAMINOR Study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Aim: Quality and quantity assessment of long-term stored (8–18 years) genomic DNA (gDNA), extracted from blood clots in BD Vacutainer Sample Separation Tubes (SSTs).
Method: Non-fasting venous blood samples were collected in the SAMINOR 1 Survey (SAMINOR 1) conducted in 2003–2004 and the SAMINOR 2 Clinical Survey (SAMINOR 2) in 2012–2014. In SAMINOR 1, 9.5 ml SSTs were used, while 8.5 ml SSTs were used in SAMINOR 2. In both surveys, serum was separated from the tubes before the SSTs with the clot were frozen in two steps, first at -20 °C and later transferred to UiT`s biobank repository for long-time storage at -35 °C. From SAMINOR 1 and 2, 15 569 and 5 975 clots, respectively, are stored in the biobank. After 8–18-year storage in biobank, 10 SSTs from each of the SAMINOR surveys were sent to HUNT Biobank (in total 20) for gDNAs extraction and quality (A260/A280, A260/A230, and DIN) and quantity assessment using Nanodrop spectrophotometer and Genomic DNA ScreenTape assay with the Agilent 2200 TapeStation system.
Results: The mean purity of gDNA, measured by A260/A280 and A260/A230 ratios for SAMINOR 1 were 1.8 and 1.9, and for SAMINOR 2 they were 1.9 and 2.1, respectively. The DIN values were 9.1 and 9.2 for SAMINOR 1 and 2, respectively. The mean yields were 225.4 ng/µl and 218.4 ng/µl from SAMINOR 1 and 2, respectively. The mean values of quality and quantity of gDNA from SAMINOR 1 were not different from SAMINOR 2.
Conclusion: gDNA isolated from SST clots stored in biobank at -35 °C for two decades, yields adequate quality and quantity of gDNA., i.e., suitable for future genomic analyses.

49: From multi-omics to better health – Managing the biological data resource in the Norwegian Mother, Father and Child Cohort Study (MoBa)

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Re-use of Data and analyses and results, Cosmos 3AB, september 12, 2024, 13.00 - 14.15

The Norwegian Mother, Father and Child Cohort Study (MoBa) is one of the world's largest pregnancy cohorts. Since recruitment began in 1999, hundreds of thousands of biological samples including blood, urine, saliva and teeth have been collected from MoBa participants and stored at the biobank at the Norwegian Institute of Public Health (NIPH). These samples were primarily collected during pregnancy and at birth, in addition to a number of follow-up collections during childhood and adolescence. The samples have since been sent to laboratories to generate biological data on important biomarkers linked to health and wellbeing. Despite their high value and hitherto untapped potential, these data have not been available for re-use to the wider scientific research community in line with the FAIR principles. Historic large scale sensitive data poses several challenges to ensure data quality, governance, and data privacy. To make data available we propose a stepwise process that incorporates legal and scientific assessment together with thorough documentation and standardization. The digital biological resource in MoBa now provides genetic, epigenomic, metabolomic, proteome and exposure data, made available for research. Combining data types across diverse omics categories linked to Norwegian health registries, allows for higher precision in identifying biological mechanisms associated with complex disease.
The biological data resource in MoBa now includes whole genome SNP-array on 235.000 participants, methylation array on 15.000 participants, metabolomics of 15.000 participants with steadily increasing overlap on data from each participant, all thanks to individual research projects. The nature of large-scale molecular data demands tailored infrastructures and management models to ensure data quality, increased availability, and ease of use.

The Hunt One Health study, a metagenomic sample and data repository for One Health-studies

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Biobank Business Models – One Health, Cosmos 3AB, september 11, 2024, 11.00 - 12.00

Animal owners in the HUNT4-study provided fecal samples from dogs, horse, cattle, sheep and pigs to an animal focused study, the HUNT One Health study. This systematic sampling of animals enabled the unique opportunity to investigate the connections between the microbiota from fecal samples of companion and production animals, with the closely associated demographic of the HUNT participants. By implementing a citizen science approach to sampling and metadata collection, we established a comprehensive sample collection to facilitate studies examining how the microbiota and genetic traits of fecal samples is relevant to animal and human health.

Fecal samples were collected from dogs, pigs, horses, sheep and cattle and deposited on fecal cards by their owners and shipped to the project office. The samples were stored upon arrival in freezers prior to further processing. Initial pilot investigations performed by the project, ensured the selection of an optimal sample processing procedure that allowed sufficient DNA to be extracted from the fecal cards. Following DNA-extraction, the DNA samples were stored in the Norwegian Veterinary Institute biobank, whilst a portion of the sample was subjected to DNA-sequencing using deep shotgun sequence technology (Illumina). The study encompassed sequencing of approximately 3000 fecal samples and controls with the resulting sequence data archived in a project database. Serving as a 'pathfinder-project' it has yielded us with important insights into requisite solutions that enable efficient use of shared physical and digital material collections.

This project's overarching goal was to disseminate material and data with other research-groups outside the project, with both samples and data currently contributing to diverse studies studying aspects of the pathobiome, resistome and microbiome-derived traits, relevant for animal and human health. Although the reusability of data and samples from the HUNT One Health study has been shown successful, we still encourage investigators to consider its use, as many important research questions remains unexplored.

The HUNT One Health study underscores the importance of adopting a One Health approach, acknowledging the potential interconnectedness of animal, human, and environmental health. Investigators from veterinary and medical research-groups interested in utilizing resources form this project are encouraged to seek access to the project material via the project page. We hope this initiative will facilitate improved knowledge dissemination and promote interdisciplinary collaborations between institutions across different sectors to address global health challenges.

51: MoBa explorer: enabling the navigation of GWAS summary statistics from the Norwegian Mother, Father, and Child Cohort Study (MoBa)

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Selected Biobank Abstracts, Cosmos 3AB, september 12, 2024, 11.00 - 12.00

Large cohort studies provide fundamental insights into human health and are key to the development of precision medicine. The Norwegian Mother, Father, and Child Cohort Study (MoBa) is a pregnancy-based longitudinal cohort that captures pivotal information concerning pregnancy and early childhood. Recently, the availability of genotyping data enabled genome-wide analysis studies in MoBa.

However, MoBa poses unique challenges for the visualization of GWAS summary statistics: (1) as a pregnancy-based cohort MoBa requires the joint visualization of paternal, maternal, and fetal association results, and (2) as a longitudinal study, association results need to be visualized over time. As a result, there is a need for novel data visualization that can help researchers navigate GWAS summary statistics over different dimensions. Additionally, accessible presentation of this information can aid in its dissemination, and communication on genetics and precision medicine. It can open access to this data to a mixed audience of experts and individuals without a specialized background.

Here, we present a dashboard that allows researchers to interactively explore MoBa GWAS summary statistics and help familiarize a non-expert audience with the study. The design was established through interviews with potential users who provided input on tasks and questions they envisioned users would have for the dashboard.

The dashboard allows users to query data by selecting variables of interest and displays information on GWAS results for different study phenotypes and time points (Fig. 1).

In addition, the dashboard aims to communicate this information to a non-specialized audience with varying degrees of biomedical literacy. It features an interactive tutorial explaining the data and the analysis process of GWAS results while guiding a user through its sections. It is based on narrative visualization techniques and provides an effective way to communicate this information to individuals without a specialized background.

In conclusion, our interface serves as a gateway to MoBa GWAS results and provides a means of interacting with the data. Hence, MoBa data becomes more easily available to both researchers and a lay audience.

52: Pediatric Biobanking of Hematological Diseases- Transitioning from an Enthusiastic Research Collaboration to a Sustainable Infrastructure

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background
The Nordic Society of Pediatric Hematology and Oncology (NOPHO) was founded in the early 1980s by a group of enthusiastic friends. The continuing goal of NOPHO is to increase pediatric cancer survival rates. In 1992, NOPHO agreed on a standardized program for pediatric cancer treatment, and began collecting samples for research. In 2006, these samples were inherited by the now formally initiated NOPHO Leukemia Biobank (NLBB). Since the beginning, sample collection has continued under a largely fragmented framework of different labs with wide variation in documentation and data storage practices. In 2019 the NLBB was moved to the already established infrastructure of Uppsala Biobank, allowing a more sustainable approach, where new efforts can be made to comply with the initiatives of today, such as the European ALLTogether1 (A2G) treatment protocol, and Genomic Medicine Sweden's (GMS) project of implementing whole genome sequencing (WGS) in Swedish healthcare, while the already established collaboration of sharing sample and associated data across boarders continues.
What does the biobank hold?
Today the biobank consists of approximately 5900 unique donors, representing citizens from all the Nordic countries. Over the years, different pediatric cancer treatment protocols have been used, and different sample types have been collected (for example PBMC, csv, serum, plasma, DNA, RNA). Sampling generally occur at diagnosis, follow ups, and in case of relapses. As of today, there is a track of 20 requests for samples that have given rise to over 40 publications.
What are the main challenges the biobank faces?
The future of the NLBB is currently challenged by both its past and its present. Not only must NLBB contend with the fragmented data infrastructure of its extant sample collection, but it must also comply with new initiatives within the field of pediatric cancer. In order to achieve a sustainable long-term infrastructure solution, NLBB must be able to effectively assure the integrity, quality, and accuracy of the samples and their associated data. In addition NLBB must establish a strong set of protocols and controls for consensus-based decision making and organizational change in order to not let history repeat itself.
What can the future hold?
To ensure consensus-based decision making the establishment of a steering committee is necessary in order to shape the future strategy and ensuring that this strategy can be feasibly implemented. In addition, with the implementation of WGS within Swedish healthcare it will be essential to create a connection between the WGS data and the biobank data, to ensure smooth access to both sample and data, while being resourceful with both funds and biomaterial.
Conclusion
In conclusion, building organizational strength and implementing stronger internal controls will help NLBB to support research in a timely and efficient manner. The risks of error, interoperability issues, and other inefficiencies will be reduced. These changes are necessary to help NLBB transition from an enthusiastic research collaboration, to a fully functioning and sustainable infrastructure that is able to comply with regulatory demands and stakeholder needs, while continuing its goal of increasing pediatric cancer survival rates.

53: A biobanking strategy for research: facilitated access to health care pathology and cytology samples

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Around half of the applications for establishment of sample collections for research refers to access to existing pathology samples collected within healthcare. In Sweden, healthcare is managed within different regions. Locally in many Swedish regions, there is a deficit in personnel resources to accommodate both the current and increasing interest from the research community.

The national infrastructure Biobank Sweden has for many years strengthened the infrastructure of research support. Today, there are established national resources helping with coordination and accessing newly collected biobank samples for national studies involving more than one region. However, this support does not include already existing pathology and cytology samples collected within the healthcare sector.

When it comes to existing healthcare samples there is a heavy workload on the local pathology laboratories within the regions to communicate with researchers/sponsors in national studies. Coordinated communication routines do not exist between laboratories over regional boarders, thereby, requests of access to healthcare pathology samples needs to be communicated with each regional pathology laboratory in parallel. In addition, working routines, existing sample types, and sample preparation methods differ between the laboratories.

Furthermore, the existing laboratory information systems (LIS) are not designed for facilitating sample access for research. This results in time consuming procedures, e.g. ensuring consent, multiple registration steps for traceability. In addition, manual individual assessment of each sample is required to ensure that enough sample remains for the patient's own care and treatment.

This combined, often leads to a time consuming and ineffective process, for both the researcher and the laboratory responsible for the samples.

To solve this issue, Biobank Sweden assigned national coordinators for biobanking strategy, dedicated to facilitating access to healthcare pathology and cytology samples for research. The primary goal was to form a national network consisting of regional contacts/study coordinators solely focusing on research requests for samples collected within the healthcare sector. This network is now established with representatives from all healthcare regions. Below are some examples of initiatives within the network that are currently ongoing:
- Form communication strategies between the already existing support units, within Biobank Sweden, that focuses on sample access for research
- Increase structured collaboration for national studies
- Create a service catalogue for research, publicly available and presenting services at each regional laboratory
- Streamlined routines for accessing healthcare samples
- Coordinated discussion with the Laboratory Information System providers in order to increase efficiency in the workflow

The goal is that this network will be beneficial to the research community. That is, help facilitating, and in the long run increasing the usage of existing pathology and cytology samples collected within healthcare.

54: BETTER4U: Preventing obesity through biologically and behaviourally tailored interventions

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The obesity epidemic constitutes a leading public health threat, currently seen as an indispensable underlying cause for the manifestation of many non-communicable diseases (NCDs). The growing prevalence of obesity and its association with poor mental and physical health outcomes renders the optimization of obesity prevention measures a public health priority. BETTER4U is designed to address the prevalence of obesity in Europe with the assistance of modern artificial intelligence (AI) technologies and the collaboration of an international, multidisciplinary group of experts.

The BETTER4U project aims to personalize the management of obesity determinants via practically assessed lifestyle recommendations tailored to the individual. The project's main objectives are to 1) map obesity determinants over the life course in cohorts spanning the geographic and cultural range of Europe; 2) develop novel AI models that integrate genetic and other omics data with lifestyle and environmental information in predicting obesity risk; 3) create a robust mechanism for applying individualized interventions for the prevention of obesity; and 4) test the effectiveness and cost-effectiveness by conducting a pilot study and a randomized clinical trial (RCT) in adults from seven European sites, in which participants will receive personalized recommendations from healthcare professionals via use of an AI platform and technologically-assisted, real-time monitoring tools.

In this talk, I will provide an overview of the BETTER4U project and our federated machine learning methodology for multi-factorial data analyses across the multiple cohorts in the project.

55: Exploring genetic clustering of severity markers to identify groups with reduced heterogeneity in multiple sclerosis

PhD Pernilla Stridh[1,2], PhD Klementy Shchetynsky[1], MD PhD Adil Harroud[1], PhD Narsis Kiani[1], Prof Lars Alfredsson[1], Prof Jan Hillert[1,2], Prof Tomas Olsson[1,2], Prof Ingrid Kockum[1,2]
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Selected young researchers' talks, Cosmos 1-2, september 12, 2024, 13.00 - 14.15

Introduction: Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder characterized by inflammation, demyelination, and axonal degeneration. MS is a complex disease with varying clinical manifestations and rate of disease progression, and is highly heterogeneous with respect to paraclinical findings, clinical outcomes, and response to treatment. The underlying etiology of MS is not yet fully understood, although both genetic and environmental factors contribute to the development and progression of the disease and largely point toward adaptive immune dysfunction. Predicting the severity and acceleration of disease progression at the time of diagnosis is virtually impossible, leaving affected individuals facing substantial uncertainty for years. Effective management of MS often requires a personalized approach, which can be enhanced by a deeper understanding of patient subgroups. Here, we explore a genetic clustering approach to reduce the heterogeneity in MS.

Aim: The aim of this study is to identify groups of MS cases who share sets of genetic, clinical and lifestyle similarities, and test if group characteristics can be used to predict severity and rate of disease progression.

Methods: We explored genetic clustering in in 10,179 persons with MS from Sweden who were part of the EU-funded MultipleMS project [EU RIA 733161] (6,589 genotyped on Illumina Human OmniExpress and 3,590 genotyped on Global Screening Array). More than 7 million variants were imputed from genotypes based on the Haplotype Reference Consortium. To nominate MS severity variants for clustering, we performed rudimentary genome-wide association (GWA) analyses of 17 parameters capturing physical and cognitive disability, central nervous system inflammation, disease progression, and radiological findings. Suggestive severity variants were used for principal component (PC) analysis, and the distribution of eigenvectors were leveraged to segment the patients into distinct subgroups. Logistic and linear regression was used to identify clinical outcomes and biomarkers enriched in patient subgroups.

Results: In total, 1,646 single nucleotide polymorphisms (SNPs) that survived suggestive $p<1x10-5$ cut-off and clumping were selected for PC analysis. Although most MS cases occupied an overlapping PC space, we identified six distinct subgroups who shared genetic loadings and specific medical history characteristics. Examining the genetics loadings for patient clusters, we identified the four genetic loci that contributed the most to these components. The inclusion origin of the markers from these loci traced back to genetic association with MS severity phenotypes Neurofilament Light and oligoclonal banding in cerebrospinal fluid.

Conclusions: We have explored clustering to identify groups of people with MS based on genetic markers of severity. The ability to separate out small clusters suggests that this approach can be expanded to reduce heterogeneity in MS and to identify outcome predictors to ultimately increase the ability to offer prognosis.

56: The APOE genotype, cardiovascular risk and all-cause mortality: The HUNT Study postpo

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background/Objectives: Cardiovascular diseases (CVDs) are the leading cause of global mortality, with the World Health Organization reporting that CVDs accounted for 32% of all global deaths in 2019. The SCORE2 risk prediction model, previously validated in the Norwegian Trøndelag Health Study (HUNT), estimates 10-year CVD-risk in Europeans without prior CVD or diabetes. Apolipoprotein E (APOE) is a gene variant associated with increased lipid-related CVD and neurodegenerative risks. In this study, we examine the interaction between CVD-risk measured by SCORE2 and APOE genotypes in predicting all-cause mortality in the HUNT cohort. This knowledge is important for future preventive strategies and personalized medicine.

Methods: We conducted a prospective cohort study including 22,997 participants from the HUNT2 (1995-1997) cohort. Participants aged 40 years or older without prevalent CVD or diabetes were included. Participants were followed until 30 November 2023 with a median follow-up time of 26,8 years. We stratified participants into low APOE risk (ε2ε2 or ε2ε3), intermediate risk (ε3ε3) or high risk (ε2ε4, ε3ε4 or ε4ε4 genotypes). SCORE2 was used to categorize further into low, medium and high CVD-risk groups. Cox proportional hazards models were utilized to determine the independent effect, expressed as Hazard Ratio (HR) with 95% Confidence Interval (CI), of APOE genotypes and SCORE2 cardiovascular risk scores on overall mortality. We then assessed the association between CVD-risk and all-cause mortality within each APOE category.

Results: APOE genotypes significantly affected mortality, with intermediate APOE risk individuals (HR = 1.14, 95% CI: 1.06 - 1.23) and high APOE risk individuals (HR = 1.30, 95% CI: 1.21 - 1.41) showing increased mortality compared to the low APOE risk group. The level of CVD-risk showed a dose-response association with mortality, with individuals in the medium CVD-risk category (HR = 1.51, 95% CI: 1.42 - 1.61) and high CVD -risk category (HR = 2.20, 95% CI: 2.02 - 2.39) experiencing increased mortality risk compared to the low CVD-risk group. CVD-risk categories distinctly influenced risk of mortality across all APOE groups. For individuals with low APOE risk, those in the medium and high CVD-risk categories experienced higher risk of premature death (HR 1.57, 95% CI: 1.30-1.92 and HR 2.56 CI: 1.98-3.32, respectively). This trend continued in the medium APOE risk group (HR = 1.60, 95% CI: 1.47-1.74 and HR = 2.51, 95% CI: 2.23-2.81 for medium and high CVD-risk categories, respectively) and was evident in the high APOE risk group (HR = 1.51, 95% CI: 1.35-1.69 and HR = 2.03, 95% CI: 1.75-2.36 for medium and high CVD-risk categories, respectively).

Conclusion: Our results demonstrate a dose-response relationship between level of CVD-risk and all-cause mortality across all APOE genotypes, illustrating a substantial increase in mortality risk irrespective of APOE status. These findings advocate for universal preventive strategies and risk assessments to manage cardiovascular risk effectively. However, future studies should incorporate polygenetic risk scores into risk prediction frameworks for the purpose of refining risks and creation of earlier and tailored CVD risk reduction strategies.

57: Meta Genome-Wide Association Studies of Time to Progressive Multiple Sclerosis

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction
Multiple sclerosis (MS) is a central nervous system (CNS) immune disease characterised by a course of relapse-remission, then steady progression. Inflammation and neural degeneration, followed by a broad spectrum of motor, sensory, and cognitive disabilities, characterise the pathology of MS. Owing to international collaboration, MS heritability for susceptibility has reached approximately 0.48; however, little is known about the genetic factors influencing the various progression manifestations in MS patients.

Objectives
This is the first large-scale international and interracial study that aims to identify genetic loci and the associated biological mechanisms underlying the time of secondary progression conversion (TimeSP) and age at progressive MS initiation (AgeP), which are important phenotypes of MS progression.

Methods
We conducted meta-genome-wide association studies using linear mixed models utilising international and interracial cohorts from Sweden, Italy, and the US. The p-value thresholds used were the conventional 5e-8 for as conventional GWAS based on European ancestry requires. The covariates for TimeSP were the year of birth and age at onset; for AgeP, they were the year of birth and sex.

Results
Our analyses suggest two loci in chromosome 6 for AgeP and chromosome 14 for TimeSP GWAS. Sensitivity analysis, adding the HLA-DRB1*1501 known for its significant association with MS susceptibility in the AgeP GWAS regression model, unchanged the significance of the locus. The AgeP GWAS lead SNP, which had the highest posterior probability of contributing to the trait in the locus, was tested for its association with AgeP in different treatment groups, categorised as low efficacy drug intake group, high efficacy drug intake group, and a group that had both drugs, showed no effect differences between the groups. SNP-gene positional, eQTL, and chromatin interaction mapping for AgeP GWAS revealed that the mapped genes are highly expressed in the brain and EBV-transformed lymphocytes. A gene set analysis for the AgeP study revealed significant involvement with the lenaour dendritic cell maturation pathway. A MAGMA gene-based test for TimeSP identified a gene associated with the trait that is actively expressed in the central nervous system.

Conclusion
Our study suggests that the genetic variants contributing to the time to progressive MS are associated with both central nervous system and immune-related biology.

58: Accurate determination of clinically relevant structural variation in the CYP2D6 locus: from SNP microarrays to long-read sequencing

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Cytochrome P450 2D6 is a liver enzyme that contributes to the metabolism of over 20% of commonly used drugs. The corresponding gene, CYP2D6, is known for being highly polymorphic. The repetitive elements flanking the gene give rise to copy number variations (CNVs), and hybrid genes can arise with a neighbouring highly homologous pseudogene CYP2D7. Here, we present results from a comprehensive comparison of complex pharmacogenetic phenotypes in the Estonian Biobank (EstBB) using microarray and whole-genome sequencing (WGS).

EstBB comprises over 210,000 individuals genotyped with Illumina Global Screening Array. Additionally, ~2,800 samples are sequenced with Illumina short reads. A set of overlapping samples have been sequenced using long reads on the Pacific Biosciences (PacBio) Revio platform (n = 16) and Oxford Nanopore Technology (ONT) PromethION (n = 48). For long-read sequencing, individuals with gene fusion events or CNVs in the CYP2D6 locus, as defined by short-read WGS, were prioritised in the selection process.

Three tools, Aldy, Stargazer, and Cyrius, were used to assign CYP2D6 haplotypes (i.e., star alleles) to short-read WGS samples. The calls exhibited a high level of concordance, with two out of three tools agreeing in 97% of the cases. Based on this consensus set, 4.3% and 1.9% of Estonian individuals carry a CYP2D6 full gene deletion (*5) or copy gain (*1xN, *2xN, etc), respectively. The most common hybrid gene is *68 (12.6%), which most often appears in tandem with a non-functional *4 allele. The *13 hybrid was either present as a single gene in 0.5% or in tandem with *2 in 0.9% of the WGS cohort. Pangu was used for star allele assignment in PacBio and ONT data. Altogether, 11 PacBio and 11 ONT samples were assigned a CNV or a hybrid gene, of which 5 and 4, respectively, were in concordance with short-read WGS. Pangu successfully identified three diplotypes, which short-reads failed to detect, including a complex diplotype *5/*68x2+*4 comprising a variety of above-mentioned alleles. Additionally, long reads revealed a rare *68+*2 tandem, whereas short reads erroneously indicated a *68+*4 configuration.

We used Stargazer to assign CYP2D6 star alleles to the full genotyped EstBB cohort. We observed high concordance (99.4%) with short-read WGS for diplotypes without CNVs or hybrid genes. Popular star allele callers cannot leverage microarray data to detect structural rearrangements, and other tools utilised for this purpose suffer from high false positive and negative rates. Nevertheless, our preliminary observations suggest unique array intensity signatures for star alleles encompassing CNVs or hybrid genes (Figure 1). We are currently developing machine learning models for improved array-based CNV discovery, with the possibility of estimating the true CYP2D6 effect for biobank participants without WGS data.

In conclusion, while long reads are essential for resolving complex CYP2D6 haplotypes, microarray and short reads provide excellent data that contribute to the advancement of personalized medicine. We anticipate that thousands of samples with long reads will allow us to assemble a unique multi-platform dataset for developing advanced methodologies to distinguish microarray-based signals corresponding to specific CNVs and hybrid structures in clinically relevant genes.

61: The Tromsø Study 1974-2024: The population-based investigation and its genetic data.

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The Tromsø Study was initiated in Tromsø municipality in 1974 to study the high cardiovascular mortality in the region. Today, seven data collection surveys have been conducted and the research focus has broadened to cover several non-communicable diseases and conditions. The study is based on complete birth cohorts and random samples of the population in 1974, 1979–1980, 1986–1987, 1994–1995, 2001, 2007–2008, and 2015–2016. A total of 45,473 participants have attended at least one of the first seven data collections and the eight' data collection will be conducted in 2025-2026. The Tromsø Study cohort is basis for both longitudinal and cross-sectional analyses as well as case–control studies and clinical trials.

The different collections have included self-administered questionnaires, measurements, clinical examinations and biological sampling of blood, urine and faeces and nasal swabs. Physical examinations include measurements of blood pressure, heart rate and anthropometry. Clinical examinations of subsamples have expanded since 1994-95 and comprise echocardiography, electrocardiogram, carotid artery ultrasound, spirometry, bone densitometry, body composition, physical function, pain sensitivity, cognitive testing, retinal photography, and dental status. An overview of available data can be accessed at helsedata.no.

The Tromsø Study is linked annually to the Norwegian Cancer Registry and the Cause of Death Registry, as well as to the national myocardial and stroke registries. The University Hospital of North Norway is the only hospital in Tromsø and has been the source for local disease endpoint registries within the Tromsø Study. Further, there are ample possibilities for linkage of the Tromsø Study with the Norwegian Patient Registry, the Norwegian Prescribed Drug Registry, and the Medical Birth Registry.

The Tromsø Study databases are now enriched with genetic data. Genetic analyses were performed for 31,280 participants who consented to genetic analyses and had available sample materials, representing 69% of those enrolled in the Tromsø Study. DNA was extracted from buffy coat samples at the HUNT Biobank, NTNU. The genotyping was performed in two main batches (2014-2015 and 2020-2021) at the NTNU Genomics Core Facility (GCF) using Illumina HumanCoreExome arrays. The processing of the genotyping results was performed in collaboration with the HUNT Centre for Molecular and Clinical Epidemiology, NTNU. The work followed a strict quality control protocol, resulting in data for 485,058 polymorphic variants. Current efforts aim to impute the genotyped data using available reference panels.

The genetic data in the Tromsø Study is comparable to genetic data available in other population-based studies in Norway. The data is stored in the HUNT Cloud service, a digital infrastructure for secure storage, access control, and research analysis of sensitive data. The genetic data will be managed as part of the Tromsø Study biomarker data. Researchers associated with Norwegian research institutions can apply for access to the data Tromsø Study data, and we welcome research collaborations with researchers at UiT.

62: Towards Precision Medicine with Blood based biomarkers - A novel automated multiplex immunoassay for the ultrasensitive detection of blood-based biomarkers for neurodegenerative diseases

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Efforts to identify accurate blood biomarkers for neurodegenerative disease hallmarks have been hampered by the lack of a proteomic tool that has the required sensitivity to detect very low concentrations of brain-derived proteins in plasma or serum and the ability to multiplex many analytes in a single assay. Here we evaluated NULISA™, a recently developed novel immunoassay with attomolar level sensitivity and high multiplex capability1, for its ability to detect serum biomarkers associated with Alzheimer's disease.

Methods: Serum samples from 31 Alzheimer's disease (AD) patients and 31 non-AD controls were analyzed using NULISA with a 200plex inflammation panel targeting a broad spectrum of inflammation-related cytokines, chemokines and other proteins. Five samples failed quality control and were excluded from further analysis, resulting in 28 AD and 29 control samples in the final dataset. Linear model analysis, including age and sex as covariates, was performed for each target for differential expression between AD patients and controls.

Results: Two significant differentially abundant proteins were identified. The level of glial fibrillary acidic protein (GFAP) was 1.84-fold higher in AD patients (adjusted p-value = 0.00014), whereas the level of S100 calcium-binding protein A12 (S100A12) was 2-fold higher in non-AD controls (adjusted p-value = 0.031). GFAP serum levels correlated strongly with total tau (Spearman rho = 0.69, p=1.7e-09), p-tau181 (rho=0.69, p=1.7e-09) and amyloid beta 42 (rho= -0.71, p=4.7e-10) levels in cerebrospinal fluid (CSF). S100A12 levels also correlated significantly with total tau (rho = -0.39, p=0.0031), p-tau181 (rho=-0.36, p=0.0053) and amyloid beta 42 (rho= 0.38, p=0.0067) CSF levels. Receiver operating characteristic analysis demonstrated that GFAP strongly discriminated AD from controls with an area under the curve (AUC) of 0.93 (95% CI 0.87-1.0), and S100A12 also exhibited good discrimination with an AUC of 0.72 (95% CI 0.59-0.86).

Conclusion: This exploratory study identified serum GFAP levels as a strong discriminatory biomarker for AD, consistent with previous studies. S100A12 also demonstrated significant associations with AD and CSF biomarkers and thus warrants further study. NULISA holds great promise for the discovery and validation of blood-based biomarkers for the early detection and monitoring of neurodegenerative diseases.

64: Pediatric Diabetes Clustering: Influence of feature standardization and use of reverse graph embedding as a complementary approach.

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction & Objective:
Diabetes mellitus manifests as a phenotypically heterogeneous disease. Patient subclassification has been tested and replicated multiple times in adults with diabetes. However, pediatric diabetes remains highly unexplored. This study aims to compare and combine different methods for subclassification of children with diabetes based on phenotypic variables and to assess the effect of using standardization in patients clustering.

Methods:
We analyzed patients from the Norwegian Childhood Diabetes Registry (NCDR), a nationwide registry which systematically registers all incident cases of childhood diabetes. Participants included both Autoantibody Positive (n=2560) and Negative (n=360) cases between 1 and 18 years of age. Participants were manually clustered based on Autoantibody detection and sex, then, k-means clustering was used to further cluster these subgroups. We compared the use of absolute values of phenotypic features versus standardization of the same variables adjusting for age and sex. Finally, as a complement to clustering, we applied a reverse graph embedding algorithm, which reduces the complex data into a low-dimensional space where diabetes can be studied as a multidimensional spectrum instead of isolated subgroups.

Results:
Autoantibody positive patients fell in two clusters. Differences derived mainly from age at diagnosis, C-peptide, and BMI. When clustering using values from the registry, patients with later diagnosis presented higher C-peptide levels and BMI. However, after adjusting the variables for age and sex, this trend reverted and later diagnosis was associated with lower BMI and C-peptide levels, demonstrating the necessity for age and sex standardization in order to capture only disease related phenotypic changes in childhood clustering. Autoantibody negative cases clustered in three groups. Cluster 1 presented the lowest levels for glucose and HbA1c and the highest age at diagnosis, C-peptide and BMI, aligning with the classical presentation of youth-onset type 2 diabetes. Cluster 2 showed a similar age at diagnosis as Cluster 1 but an opposite phenotype, with the highest glucose and HbA1c levels and the lowest C-peptide and BMI. Cluster 3 presented the youngest age at diagnosis and values in between Cluster 1 and 2 for the rest of the variables. Adjusting for age and sex led to strengthened cluster number prediction, increased cluster stability, and improved cluster homogeneity. Finally, the use of reverse graph embedding allowed a more nuanced analysis of cases at the interface of clusters, and proved valuable when assessing the distribution of a specific phenotypic attribute.

Conclusion:

Pediatric diabetes phenotypic clustering results in different subtypes. These subgroups differ from those derived from adults. Adjusting for age and sex leads to a more precise subclassification, projecting out age and sex components and focusing on disease-specific phenotypes. Finally, the use of reverse graph embedding allows for a finer analysis of the different phenotypic traits, which may improve patient characterization and treatment selection.

66: Global Long COVID Host Genetics Initiative

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Selected young researchers' talks 2, Cosmos 1-2, september 12, 2024, 14.30 - 15.00

Introduction: Infections, including SARS-CoV-2, can cause long-term health problems beyond the acute disease. The response to COVID-19 varies significantly among individuals, in some cases leading to prolonged symptoms such as fatigue, dyspnea, cognitive dysfunction, and sleep disturbances. To shed light on the genetic underpinnings of these persistent symptoms, we established the Long COVID Host Genetics Initiative—a global collaborative effort.
Materials and Methods: 24 studies from 16 countries, representing 6 genetic ancestries, worked together to define Long COVID using questionnaire data on symptoms and recovery from COVID-19, or electronic health record data with specific diagnosis codes for post COVID-19 conditions. Subsequently, all contributing studies conducted genome-wide association analyses (GWAS) comparing Long COVID (N=6,450) to subjects recovered from COVID-19 (N=46,208) or population controls (N=1,093,995).
Results: A cross-ancestry meta-analysis of Long COVID after test-verified SARS-CoV-2 (N = 3,018) and population controls (N = 994,582) identified a haplotype spanning the genomic region chr6:41,512,355-41,537,458 associated with increased risk for Long COVID (lead variant rs9367106, P = 1.8×10-10, odds ratio = 1.63, 95% confidence interval: 1.40-1.89, risk allele frequency = 4.2%). The association replicated in an independent sample of nine studies with 9,500 Long COVID cases and 798,835 controls.
Additionally, a variant (rs12660421-A) within the Long COVID risk region was linked to increased FOXP4 gene expression in the lung (P = 5.3×10-9, normalized effect size (NES) = 0.56) and in the hypothalamus (P = 2.6×10-6, NES = 1.4) in GTEx dataset. The association signals for Long COVID and differential expression of FOXP4 in the lung colocalized with posterior probability (pp) = 0.91. Variants in the FOXP4 region have earlier been associated with the severity) of acute COVID-19 and lung cancer, and a colocalization analysis demonstrated these signals were shared (pp = 0.97 and 0.98, respectively). Mendelian Randomization supported the role of COVID-19 severity as a causal risk factor for Long COVID (p = 2.4×10-3). However, most Long COVID patients had a mild or moderate initial disease, and in a Bayesian analysis FOXP4 was found to be more strongly associated to Long COVID than the severity of acute COVID-19.
Conclusions: Our global collaboration has unveiled the first genome-wide significant association for Long COVID. The risk locus upstream of the FOXP4 gene on chromosome 6, previously linked to acute COVID-19 severity and lung functions, colocalizes with an expression quantitative trait locus (eQTL) in the lung. Our results suggest a role for lung functions and immune system regulation in Long COVID pathophysiology. eQTL in the hypothalamus may contribute to the aetiology of fatigue and sleep-related symptoms. Severity of acute COVID-19 increases the risk for Long COVID, but further analyses comparing the effects of FOXP4 locus and other severity variants suggested that the FOXP4 association with Long COVID extends beyond acute COVID-19 severity alone.

Acknowledgements: We acknowledge the contribution of healthcare professionals, technicians, patients and researchers working hard together to tackle the pandemic and its long-term consequences. The full list of authors contributing to the Long COVID Host Genetics Initiative can be found in our preprint in medRxiv:
https://www.medrxiv.org/content/10.1101/2023.06.29.23292056v1.full-text

67: microRNA as biomarkers in early detection and personalized treatment in ovarian cancer: Development of a personalized prevention consortium

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Biospeciment Science, Sample Handling and Quality, Cosmos 3AB, september 11, 2024, 14.00 - 15.15

Epithelial ovarian cancer (EOC) has poor survival given that there are no effective early detection strategies and non-specific early disease symptoms; thus, the disease is largely diagnosed at advanced stage, after the disease has spread. Our recently completed work shows significantly better survival with earlier stage at diagnosis for even the most aggressive EOC subtypes, underscoring a potential benefit of earlier detection.

We are working to address the challenges of earlier detection of this lethal malignancy using biospecimens from biobanks with prospective cancer follow-up, together with clinical samples. To that end, we have formed a consortium with European and American partners to provide the necessary validation of a microRNA (miRNA) panel for earlier detection of EOC using serum samples and data from prospective cohorts, paired with clinical data and serum and tumor samples from hospital-based biobanks. Our objectives are to validate a serologic miRNA panel that, together with the current “best available” marker, would have sufficient diagnostic discrimination to be used as a tool that, complementary to imaging, would allow early identification and stratification of patients with suspected malignancy to personalized gyn-oncological care. We will:

*Validate serum miRNA profiles as biomarkers for early detection in samples collected from cases <=3 years prior to EOC diagnosis and matched controls and characterize sources of variation in miRNA profiles and their impact on discrimination.

*Evaluate miRNA profiles in the clinical setting and the discrimination between EOC cases and women with (i) benign ovarian tumors in blood samples collected prior to diagnostic surgery and (ii) underlying comorbidities (including other cancer types). Further, we will evaluate serum miRNA profiles as predictors of recurrence and will compare tumor tissue and serum miRNA profiles.

*Develop and optimize protocols for data integration and methods for algorithm development. Direct in silico validation, including miRNA and CA125 levels, and clinical and epidemiologic data.

*Address Ethical, Legal and Social Aspects (ELSA), including activities in key stakeholder groups. Challenges in health data privacy and sharing, including for development of an artificial intelligence model, will be addressed, as will the definition of a “healthy” population with respect to miRNA profiles for EOC.

The consortium was launched in 2023, with first findings expected in late 2024. Beyond the initial direct aims of the consortium, expanded aims on further promising markers are envisaged. This work is part of an overarching research program on EOC across the prevention spectrum, from risk through survival, toward reducing mortality from this malignancy.

68: Finnish Hematology Registry and Biobank (FHRB): a national population-based comprehensive biobank resource for hematological research

Phd Tiina Vesterinen[2], Satu Koskela[1], Prof Maria Buchert[3], Prof Eeva-Riitta Savolainen[4], Phd Kimmo Pitkänen[1], Phd Marja Sankelo[5], Phd Mika Kontro[6]
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Abstract:

Objectives. Biobanks accelerate research by providing a readily accessible resource of well-annotated, high-quality patient samples. The objective of the Finnish Hematology Registry and Biobank (FHRB) is to promote the development of new methods for diagnostics and treatment of hematological disorders.

Research question. FHRB was established in 2014 as a non-commercial, disease-focused, nationwide source of patient material for research purposes. As hematological disorders are rare diseases, a national repository of biobank samples is required for a representative collection and resource. Here we describe the status of the biobank.

Materials and methods. After attaining an informed consent from the patient, bone marrow, blood and skin biopsy samples are collected at diagnosis, remission, and relapse(s). Bone marrow samples are subjected to density gradient separation after which mononuclear cells (MNCs) are stored as viable cells and cell pellets. Blood samples are centrifuged and serum or plasma are separated. Skin biopsies are frozen as such. All samples are stored in liquid nitrogen and their quality is assessed at regular intervals. Comprehensive clinical information is recorded into a structured clinical registry. The sample and data collection are available world-wide to all researchers, whether academic or industrial. An independent, international panel of experts evaluates all applications with the main criteria being scientific excellence and feasibility of the proposal.

Results and Conclusion. As of April 2024, FHRB administers a collection of >24 000 samples from more than 3000 patients. Three of the most common diagnoses are acute myeloid leukemia (30% of the samples), multiple myeloma (22%) and acute lymphoblastic leukemia (19 %). 66% of the samples were collected at the time of diagnosis. Operations of FHRB are based on standard operating procedures. In sample quality assessment of 186 viably frozen bone marrow MNC samples tested by June 2023, median RNA yield was 5.1 µg with median RIN value of 9.6. The median cell viability after thawing was 88%. To date, FHRB has granted over 5 100 samples from more than 2300 sample donors to 29 applicants. The most popular sample type has been viable frozen bone marrow MNCs from acute leukemia patients.

To conclude, the Finnish Biobank Act together with nationwide collection of samples and data enable FHRB to offer comprehensive, high-quality samples with clinical annotation for hematological research and development. FHRB is currently one of the largest hematology-focused biobanks and has a robust operating, funding and governing structure ensuring a long-term sample resource for rare hematological disorders.

69: The Interplay Between Birth Weight and Obesity in Determining Childhood and Adolescent Cardiometabolic Risk

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Cardiometabolic Disorders I: Growth and obesity., Cosmos 1-2, september 11, 2024, 14.00 - 15.15

Background: Birth weight (BW) is associated with risk of cardiometabolic disease (CMD) in adulthood, which may depend on the state of obesity, in particular if developed at a young age. We hypothesised that BW and a polygenic score (PGS) for BW are associated with cardiometabolic risk profiles and circulating plasma proteins levels in children and adolescents. We aimed to determine the modifying effect of obesity on these associations.

Methods: We used data from The HOLBAEK Study with 4,263 participants (median [IQR] age, 11.7 [9.2 , 14.3] years; 57.1 % girls and 42.9 % boys; of which 48.6% were from an obesity clinic and 51.4 % from a population-based group. We gathered information on BW and gestational age, anthropometrics, cardiometabolic risk factors, calculated a PGS for BW, and measured plasma protein levels using Olink Inflammation and Cardiovascular II panels. We employed multiple linear regression to examine the associations with BW as a continuous variable and performed interaction analyses to assess the effect of childhood obesity on cardiometabolic risk profiles and plasma protein levels.

Findings: BW and a PGS for BW associates with cardiometabolic risk and plasma protein levels in childhood and adolescence. Paediatric obesity modifies the associations between BW and measures of insulin resistance, including HOMA-IR (βadj [95% CI per SD] for obesity: -0.12 [-0.15 , -0.08]; normal weight: -0.04 [-0.08 , 0.00]; Pinteraction = 0.004), c-peptide (obesity: -0.11 [-0.14 , -0.08]; normal weight: -0.02 [-0.06 , 0.02]; Pinteraction = 5.05E-04), and systolic blood pressure SDS (obesity: -0.12 [-0.16 , -0.08]; normal weight: -0.06 [-0.11 , -0.01]; Pinteraction = 0.0479). Paediatric obesity also modifies the associations between BW and plasma levels of 14 proteins (including IL15RA, MCP1, and XCL1; Pinteraction < 0.05).

Interpretation: We identify associations between lower BW and adverse metabolic phenotypes, particularly insulin resistance, hypertension, and altered plasma levels of cytokines and adipose tissue-related proteins, which are more pronounced in children with obesity and may emerge during puberty period. Developing effective prevention and treatment strategies for this group is needed to reduce the risk of future CMD. Funding: Novo Nordisk Foundation (NNF15OC0016544, NNF0064142 to T.H., NNF15OC0016692 to T.H. and A.K., NNF18CC0033668 to S.E.S, NNF18SA0034956 to C.E.F., NNF20SA0067242 to DCA, NNF18CC0034900 to NNF CBMR), The Innovation Fund Denmark (0603-00484B to T.H.), The Danish Cardiovascular Academy (DCA) and the Danish Heart Foundation (HF)

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71: The association between clinically evaluated cognitive function and oral health in Norwegian older adults: The HUNT Study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: The relationship between cognitive function and oral health is unclear. The aim of this study was to investigate the potential association between cognitive function and oral health, both assessed by clinical experts, in a home-dwelling Norwegian older adult population.
Methods: This cross-sectional study included 633 participants aged 70 years or older from the fourth survey of the Trøndelag Health Study in Norway, specifically the HUNT4 Oral Health Study and HUNT4 70+. Cognitive function was assessed by clinical experts according to the DSM-5 criteria. Oral health evaluation was thoroughly conducted by trained and calibrated specialists in dentistry. Negative binomial regression was used to compute ratios of means (RMs) with 95% confidence intervals (CIs) for the count variables. Poisson regression was applied to evaluate prevalence ratios (PRs) with 95% CIs for periodontitis.
Results: The prevalence of neurocognitive disorders (NCDs) was 35.5%. NCDs were associated with about 20% increased mean number of dental caries. In further analyses, participants with dementia had a 9% decrease in the mean number of natural teeth compared to those with normal cognitive function. There was no clear association between NCDs and severe periodontitis.
Conclusion: Older adults with NCDs had a higher number of dental caries than those with normal cognitive function, and participants with dementia had fewer natural teeth. The study suggests the need to improve the oral health care of home-dwelling older adults with NCDs.

72: Customized genotype-based selection of fresh living cells for biomedical research from blood donor biobank

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Re-use of Data and analyses and results, Cosmos 3AB, september 12, 2024, 13.00 - 14.15

Finnish Red Cross Blood Service Biobank collects samples and data from donors that are eligible to donate blood. Since 2017 more than 70 000 blood donors nationwide have given their consent to the biobank. The sample collection includes DNA, serum, plasma and PBMCs. Fresh whole blood samples and living mononuclear blood cells (buffy coats) are also available on request. Health-related data and blood donation data are available from each biobank donor.

The Blood Service Biobank has provided 58 000 individual DNA samples for the FinnGen initiative. FinnGen is a national research project in genomics collecting samples and health data from ~10% Finnish population https://www.finngen.fi/en investigating the genetic basis of diseases with the aim of better treatment and disease prevention. Genomic data from 500 000 individual DNA samples was generated using the FinnGen ThermoFisher Axiom custom array with 665 000 genetic markers. The sample-related genomic data of blood donors have already been returned from the FinnGen project to the Blood Service Biobank.

Genomic data has enabled the Blood Service Biobank to offer not only customized genotype-based sample and data collections, but also the possibility to refine genomic data for the specific needs of future research projects. As an example, by using HIBAG computational algorithm with FinnGen genomic data and Finnish population specific imputation model (Ritari et al 2020) we have determined the HLA type “in silico” for tens of thousands of the Blood Service Biobank donors.

HLA data and fresh cells are essential in a wide range of research settings, including cancer, infectious and autoimmune diseases. For such purposes, but not limited to, the Blood Service Biobank can provide fresh immune cells donated by blood donors with specific HLA type. Eligible blood donors are screened and selected with an in-house script from the same day blood donation database based on valid biobank consent and HLA type. Blood units donated throughout the country are transported overnight to Blood Service headquarters. Buffy coat layer (40 ml) of blood units carrying the required HLA type is separated as part of the normal production process and delivered to the biobank. Buffy coat byproducts are released for research purposes in less than 24 hours after blood donation. These cells, accurately characterized for HLA factors, are particularly useful in research projects with immunologically tailored research designs aiming at personalized medicine.

HLA selected fresh blood donor buffy coat cells from the Blood Service Biobank have been crucial in a research project designing oncolytic viruses that infect cancer cells and help to kill the tumor cells (Chiaro et al 2023); mini tumors from patients were cultured with HLA matched blood donor cells to test whether these complex immune organoids can be utilized to predict a patient’s sensitivity to novel therapies. As a result, a pre-clinical human model for therapeutic cancer vaccination were established enabling highly personalized immunotherapies.

73: Returning genetic risk information from biobank to blood donors – hemochromatosis

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Selected Biobank Abstracts, Cosmos 3AB, september 12, 2024, 11.00 - 12.00

Background
The Finnish Red Cross Blood Service Biobank is specialized in transfusion medicine related questions, such as blood donor health. Vast majority (99,5%) of the biobank donors in Blood Service Biobank have given their consent to receive findings relevant to health. Post donation iron supplementation is routinely offered to all frequent donors and to women under 51 years, except donors with clinical hemochromatosis. HFE C282Y allele in homozygous form is the most common cause for hereditary hemochromatosis in Caucasian population. In homozygous form HFE C282Y is recommended to be returned by American College of Medical Genomics.

Aims
The aim of the study was to return genetic risk information to blood donors, guide them to health care for further testing and to research their experience of receiving genetic risk information. In addition, the aim was to understand if high iron storage values were found in these donors and if clinical hemochromatosis diagnose was set to donors. The ultimate goal is to prevent the provision of post donation iron supplementation in future blood donations among these donors.

Methods
Altogether 94 HFE C282Y homozygotes were identified in blood donor population, N=43 688, based on genotyping array results. Preliminary findings were confirmed with clinical grade laboratory method in an accredited subcontractor laboratory of those donors that had DNA sample in the Biobank, N=89. Identified blood donors were informed of their genetic risk for hemochromatosis by letter and guided on further consultation and testing to health care. In addition, 55 donors were invited to fill in on survey based on their experience on receiving potential risk of the disease and laboratory results performed in health care.

Results
100% of the primarily identified HFE C282Y homozygotes were confirmed with clinical grade method. So far 54,5% of the invited donors have participated in the survey. The results are preliminary and based on self-reported survey results. Of those that reported health care results, 69% had ferritin levels (S/P-Ferritin) >50, 71% had transferrin saturation (fP-Trfesat) >30% and 37% were diagnosed with clinical hemochromatosis (ICD10:E83.1). Vast majority of the donors stated they received enough information and guidance during the process, that they'd wish to receive similar information in future should kind of information appear and that genome data in biobanks should be used more widely to promote health.

Conclusion
We demonstrate a high occurrence of blood donors not being aware of their genetic risk for hemochromatosis and a relatively high proportion receiving a clinical diagnosis based on this study. Based on donors' perspectives in this study, there is a high willingness to receive genetic risk information and strong support for the use of genetic data in biobanks to promote health. However, the study data in this study is relatively small, hence more studies are needed to fully understand blood donor's views on the matter. In addition, we show that biobank material can be used for personalized blood donation policy, such as not supplying post donation iron supplementation for HFE C282Y homozygous donors.

Keywords: Hemochromatosis, Biobank, Genetic Risk, Precision medicine

75: Genome-wide association study reveals the unique genetic structure of active blood donors

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Blood donors are considered as an excellent option for healthy control cohort in genetic research. Voluntary and often frequent and continuous blood donation provides unique possibilities for longitudinal sampling. However, meeting the blood donation eligibility criteria, leads to a highly selected population, so called healthy donor effect, HDE. In addition, blood group-based donor recruitment may result in enrichment of certain blood group antigens, with well-known disease associations, in a donor pool.

To reveal the genetic qualities of blood donors and to understand the possible genetic impact of the healthy donor effect, we conducted a genome-wide association study (GWAS) between FRCBS Biobank, consisting of mainly active donors with long donation career, and a mainly hospital-based population, FinnGen. Moreover, our aim was to discover genetic variants possibly effecting blood donor health.

Additive GWAS was performed for 53,688 blood donors and 228,060 controls using Regenie v2.2.4. Sex, age, BMI, first ten principal components, birth region, and FinnGen genotyping array version were used as covariates. All the genome-wide significant ($p<5e-08$) hits were fine-mapped using SuSiE. Further association analyses were conducted on fine-mapped variants and blood groups, hemoglobin, and HLA. Genetic correlation on phenotypes previously studied in FinnGen was performed with LD Score Regression v1.0.1. Protein quantitative trait loci (pQTL) analysis was performed using multiplex antibody-based immunoassay database and multiplex aptamer-based immunoassay database, Olink and SomaScan, respectively, to detect statistically significant associations between GWAS hits and protein expression levels.

GWAS revealed 2973 genome-wide significant ($p<5e-08$) genetic loci associated with blood donorship. After fine-mapping, 5 coding and 36 non-coding variants were detected. Strongest association was seen in blood group genes ABO in chromosome 9, Kell in chromosome 7 and rs55794721 in chromosome 1 which is associated with Rh antigens. Strong associations were seen in blood donors in iron metabolism: risk towards hemochromatosis conferred by putative novel rs9968910 and lower allele frequency of iron deficiency anemia risk increasing RNF43 variant. There was negative correlation between blood donorship and phenotypic traits such as mental disorders, pain disorders, cardiovascular diseases, addiction disorders, autoimmune disorders, and Alzheimer's disease. Several HLA-alleles were detected by HLA association analysis, i.e., the well-known autoimmune risk allele HLA-DRB1*04:01 ($p=5.8e-15$) and HFE C282Y associated HLA-B*07:02 ($p=8.e-08$). 112 different statistically significant (FDR≤0.05) protein expression level variations were detected by the pQTL analysis, which resulted in enrichment of several biological processes.

We demonstrate, to our knowledge for the first time, the genetic impact of the HDE and blood group-based selection of blood donors. Apparently, the genetic basis of HDE is not limited to immediate blood donorship inclusion criteria. Studies using blood donors e.g., as a control population, need to account for the unique genetic structure of active blood donors. This can be a benefit or a challenge as many, potentially confounding, conditions are rarer among blood donors than in a normal population. In addition, the enrichment of certain blood group antigens in the

blood donor population, should be considered in research settings. Moreover, the results reveal genetic factors affecting on blood donor health and donation suitability.

76: Exploring the impact of exclusion criteria on the genetic architecture of Major Depressive Disorder in Danish biobanks

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Genome-wide association studies (GWAS) for Major Depressive Disorder (MDD) require large samples, with recent studies including more than a million individuals. However, achieving these large numbers means that inclusion criteria for cases is often relaxed, often to a single self-report item. This can impact our ability to identify core disease mechanisms. Previous research indicates that the genetic architecture of MDD differs when “shallow” criteria are used as compared to more careful clinical criteria. In this study, we aim to use Danish health registers with long follow-up to survey a life-course medical history of individuals diagnosed with MDD to identify cases with varying clinical profiles.. We study 50,000 MDD cases and 300,000 controls from three Danish biobanks linked to National register data: the iPSYCH2015 case-cohort study, the Danish Blood Donors Study, and the Copenhagen Hospital Biobank.

We conducted a comprehensive analysis to determine how different criteria for enrollment and exclusion can impact the inferred genetic architecture of MDD. We studied the prevalence of potentially exclusionary diagnoses in the broadest possible MDD (BP-MDD), which required only one or more lifetime diagnoses of ICD10: F32-33. Exclusionary diagnoses mirror enrollment requirements for deeply phenotyped clinical studies, such as lifetime exclusions for schizophrenia, bipolar disorder, or intellectual disability, post-exclusions for MDD onset subsequent to a dementia or terminal illness diagnosis, event-based exclusions of MDD occurring within one year of an AUD, DUD or MCI diagnosis, and age-based exclusions for MDD onset before 18 or after 50.

We used GWAS and SNP-based variance components analysis to compare the genetic architecture of BP-MDD to clinically plausible MDD, defined by the above criteria with or without age restrictions (CPA-MDD and CP-MDD, respectively). We then used polygenic score (PGS) profiles to test for differences in underlying genetic liability between cases with and without each potential exclusion criterion. Finally, we compared the replication sensitivity of 250 index SNPs of previously identified MDD loci to inclusion/exclusion criteria.

We observed that excluding MDD cases due to clinical enrollment considerations led to differences in the number of cases for BP-MDD, CP-MDD, and CPA-MDD (23,608, 17,199, and 7,922, respectively). Based on this, we observed an impact on GWAS power, replication sensitivity, and PGS profiles of individuals diagnosed with MDD. For instance, we observed that the PGS for ADHD was higher in CP-MDD than in BP-MDD, while the PGS for MDD, SCZ, ADHD, PTSD, and BPD were lower. In line with this, some variants increased in effect sizes when replicated in the narrower, more strictly defined CPA-MDD, while others were diminished when moving from BP-MDD to stricter CPA-MDD. This study highlights the impact of life-course exclusion criteria in defining MDD cases from biobanks on the underlying genetic architecture. We believe this motivates important discussions regarding the next steps for MDD GWAS that could help improve the portability of results across cohorts and enable.

77: Genomics and Proteomics of Heart Disease Risk Prediction in the Trøndelag Health Study

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Biobanks, Research, Innovation, Precision Medicine as a foundation of future health, Cosmos 1-2, september 10, 2024, 13.20 - 15.10

Introduction

Cardiovascular diseases remain the leading cause of death globally despite the progress in understanding genetic and environmental risk factors. Better prediction of CVD risk helps to minimize years of life lost and reduces the global burden of CVD through early interventions such as cholesterol-lowering medications and lifestyle modifications. Clinical risk prediction models for CVD, such as SCORE2, are designed for primary prevention in middle-aged adults (40-79 years). However, the incidence of first AMI (e.g. heart attack) at a young age (40-50 years) or very young (<40 years) is increasing. Exposure to risk factors over a lifetime causes irreversible vascular changes, so early intervention is particularly important.

Methods

We combine array genotypes and imputed dosages, biomarkers, international classification of disease diagnosis codes, and questionnaire data in 66,631 individuals of European ancestry from the Trøndelag Health (HUNT) Study. We identified 1,723 prevalent and 7,206 incidents of coronary artery disease (CAD). With a baseline in either HUNT2 (1995-97) or HUNT3 (2006-08), the median overall follow-up time is 20.8 years. The median age of participants is 47 years and the sample is 52.8% female. We calculated a PGS for CAD using a published score, metaGRS, with over 1.7 million genetic markers (Inouye et al, 2018). Multivariable logistic regression and Cox proportional hazards regression were implemented to test for associations between PGS and CAD. The sample was stratified by sex and age over/under 45 years. We also evaluated associations when adjusting for conventional clinical risk factors of SCORE2 such as cholesterol, blood pressure, and smoking status and self-reported family history of heart disease.

Results

The PGS was significantly associated with CAD in HUNT with a disease prevalence >20% in individuals in the top decile of the PGS distribution compared to <10% in the bottom decile. In women under 45 years of age at baseline, the hazard ratio per standard deviation of the PGS was 1.74 (95% 1.53,1.98). In women over 45 years, the hazard ratio decreased significantly to 1.24 (95% CI 1.20-1.29). Similarly for men, the hazard ratio per standard deviation of the PGS was higher in men under 45 years compared to over 45 years (1.67 [95% CI 1.54-1.82] versus 1.31 [95% CI 1.27-1.35]). The estimated effect of the PGS decreased, but not significantly so, as clinical risk factors were added to the model. For women under 45 years, adding PGS to clinical risk factors increased Harrell's C-index from 0.79 to 0.81, and for men under 45 years from 0.80 to 0.81. We also demonstrate the additive relationship between self-reported family history and PGS.

Conclusion

These results demonstrate the importance of a PGS for estimating CAD risk in men and women under age 45. We are currently replicating these findings in the UK Biobank and assessing proteomic signatures of CAD as additional predictors beyond traditional clinical risk factors and PGS. This

research provides a foundation for a precision medicine approach for CVD prevention focused on better lifetime risk prediction in individuals less than 45 years of age and women.

78: Evaluating the Predictive Ability of Polygenic Risk Scores for Intrahepatic Cholestasis of Pregnancy in the Estonian Biobank

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Precision perinatal and newborn medicine, Cosmos 1-2, september 11, 2024, 11.00 - 12.00

Background: Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder occurring in the late second and early third trimester of pregnancy, characterized by elevated liver enzymes and severe itching. The condition poses significant risks to both maternal and fetal health. Recent studies have identified genetic factors contributing to ICP susceptibility, providing an opportunity to evaluate the predictive value of ICP polygenic risk scores (PRS).

Methods: Utilizing the genome-wide association study (GWAS) summary statistics including 1,138 cases and 153,642 controls with European ancestry (Dixon et al., 2022), we calculated PRS for ICP for the participants of the Estonian Biobank using PRS-CS. Our analysis included 1,103 women with ICP diagnosis (ICD-10 code O26.6) along with 46,627 female controls who had delivery-related ICD-10 codes (confirming their pregnancy), but no ICP. The association between ICP risk and 10 PRS quantiles was modeled using logistic regression adjusted for age at recruitment and the first ten genetic principal components to control for population stratification.

Results: The ICP prevalence increased with the PRS quantiles, with the individuals in the highest PRS decile having a prevalence rate of 2.08%, compared to 0.32% in the lowest decile, showing a strong association between the PRS quantile and ICP prevalence. The odds ratio corresponding to the highest PRS decile (top 10%) compared to the lowest decile was 6.97 (95% confidence interval 5.10 - 9.76, p=5.8×10-32). Comparing the highest decile to the average (40%-60% deciles), the odds ratio was 3.24 (95% confidence interval 2.68 - 3.92, p=4.0×10-34).

Conclusions: Our preliminary findings demonstrate that PRS can be a potential tool for predicting the risk of developing ICP. These scores help to identify high-risk women and enhance monitoring strategies, potentially leading to better maternal and fetal outcomes. We are planning to continue our analysis by assessing the risk of developing ICP during pregnancy in different PRS quantiles.

References:
Dixon, P.H., Levine, A.P., Cebola, I. et al. GWAS meta-analysis of intrahepatic cholestasis of pregnancy implicates multiple hepatic genes and regulatory elements. Nat Commun 13, 4840 (2022). https://doi.org/10.1038/s41467-022-29931-z

80: A plasma protein-based risk score to predict hip fractures

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Hip fractures are associated with significant disability and mortality. Since there are effective treatments to reduce hip fractures, identification of patients at high risk of hip fracture is important to inform efficient intervention strategies. To obtain a new tool for hip fracture prediction, we developed a protein-based risk score based on 18 plasma proteins associated with incident hip fractures in the Cardiovascular Health Study (3,171 participants; 456 incident hip fractures, SomaScan 5K aptamer-based proteomic platform). The proteomic risk score predicted incident hip fractures and improved hip fracture discrimination in two Trøndelag Health Study (HUNT) validation cohorts (in total: 5,127 participants, 334 incident hip fractures; SomaScan platform). When transferred to an antibody-based proteomic platform (Olink), with 13 of the included proteins available, in a UK Biobank validation cohort (50,876 participants; 686 incident hip fractures), the proteomic risk score was strongly associated with hip fractures (Hazard Ratio per SD increase in proteomic risk score: 1.64 and 95% confidence intervals 1.53-1.77). The proteomic risk score, but not available polygenic risk scores for fractures or bone mineral density, improved the C-index beyond the Fracture Risk Assessment Tool (FRAX), which integrates information from clinical risk factors (C-index: FRAX 0.735 vs. FRAX + proteomic risk score 0.776, P=5.4 x 10^-9).

In conclusion, the proteomic risk score enhanced hip fracture prediction and discrimination in three separate validation cohorts analyzed by two substantially different proteomic platforms. The developed proteomic risk score constitutes a new tool for stratifying patients according to hip fracture risk.

81: Biobanking and sample processing in the IMPRESS-Norway study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

IMPRESS Norway is a national, clinical cancer research study. The study offers all patients with advanced, incurable cancer a targeted treatment based on the patient's molecular gene changes in the tumor. This is precision diagnostics; focusing on the molecular profile instead of the location of the cancer. The IMPRESS study has close collaboration with the diagnostics, InPreD. Patients are offered an extended gene panel analysis which maps 523 genes in the cancer tumour. This panel is called TSO500 (TrueSight Oncology 500) and covers the majority of the most common gene changes in cancer tumors for which there is treatment.

Our role in this study is to receive, process, analyze and biobank study material. In addition, we coordinate shipment of blood test kits to the study centers. The sample material we analyze are blood samples and fresh-frozen tumor biopsies. At screening level, plasma from Cell-Free DNA BCT STRECK tubes is used for ctDNA analysis. This is compared with the DNA profile analyzed by the TSO500 gene panel. Whole-genome sequencing is analyzed on the biopsies taken at various times in the study. Our task will be to slice, isolate DNA and RNA manually before it is prepared for sequencing. Quality assurance of the pre-analytical value chain is important to achieve reliable results and is therefore a large part of our everyday work.

82: Large-scale protein-disease risk association analysis in the UK Biobank: Introducing an extensive and freely available research resource in Olink® Insight

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[1]Olink Proteomics

Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Thanks to increased sample throughput and highly parallelized assaying capabilities, proteomics has emerged as an indispensable tool in biomarker discovery for the detection, prognosis, and treatment of disease. Its impact on healthcare in general and precision medicine specifically is expected to continue to grow.

The UK Biobank (UKB) Pharma Proteomics Project (PPP) represents the prime example of large-scale proteomics, with protein level quantification of plasma samples from more than 50,000 individuals. Based on Olink® Explore technology, UKB-PPP has generated data on nearly 3,000 proteins for this vast cohort. When combined with e.g., genomic or healthcare data in UKB, the opportunities for biomarker research in biology and medicine are tremendous.

This study aimed to estimate the future risk of a large and diverse set of diseases for all protein biomarkers available in UKB, thus generating a library of protein-disease risk associations freely available to researchers worldwide.

In total, 107 diseases, including e.g., cancers, neurological, and cardiovascular diseases, were selected from the PheWAS ontology and mapped to diagnosis codes from longitudinal hospital records, cancer registries, and death registries in UKB. A cohort was created for each disease, consisting of all incident cases within 10 years from the time of blood sampling as well as a set of matched, randomly selected controls with no occurrence of the disease during follow-up. All individuals with a first occurrence of the disease prior to their blood sample were excluded. For each protein, the association between measured plasma levels and the time to first occurrence of the disease was estimated using Cox regression, adjusting for sex, age, body mass index, and smoking status. In total, over 300,000 protein-disease risk associations were quantified in terms of hazard ratios with associated p-values.

Our results reveal a large heterogeneity in strength and number of associations both across diseases and proteins. Some proteins, for example growth differentiation factor 15 (GDF15) and WAP four-disulfide core domain 2 (WFDC2), have statistically significant associations to a high proportion of all included diseases, suggesting they might be less suitable as targeted biomarkers. Several other strong associations identified here, including TNF receptor superfamily member 13B (TNFRSF13B) with leukemia and neurofascin (NFASC) with type II diabetes, have been previously reported in independent research, which provides a basic level of validation.

The complete set of results has been made freely available via Olink Insight, an online portal to support proteomic research. With its broad coverage of diseases and its large pool of UKB data as foundation, this new resource can enhance future studies. For example, our results can help guide biomarker selection for a given disease of interest or be used to cross-reference findings in the post-study analysis phase.

84: Engagement with children from marginalised communities in India regarding gene research and tailored treatments for children's asthma and allergy. pos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

There is a need for substantial user engagement with research involving biobanks developing tailored treatments, so that the key principles of precision medicine, and its differences with standard care, are fully appreciated by users. Our systematic review (2019) indicated that such user engagement is taking place in the Global North with little involvement in countries within the Global South.

In the UK, we have created a biobank for children's asthma and allergy which has driven exploratory research for two decades. The work led to randomised controlled trials showing improvements in childhood asthma-related outcomes with precision medicine-led interventions. We are currently exploring pathways with the UK NHS Pharmacogenomics Network for implementation in clinical settings. Work in India on similar lines is driving the development of biobanks, and we want to collaborate with these groups for children's asthma and allergy research. Hence, we planned user engagement events with topics that underlie precision medicine-led treatments in children's asthma and allergy.

The research team and students designed demonstrations to discuss allergy-related disease and share these novel precision medicine concepts with children. The engagement events were held in one urban and two rural schools in West Bengal, India. We worked with children and young mothers, including families of farm workers. A total of 239 children (5-14 years) participated in the events. 239 feedback forms were received. Some mothers joined with their children for one of the rural sessions.

We created, for example, a demonstration of the skin barrier with sand, a sieve and Vaseline, to show how tailored treatments could benefit a proportion of children who have loss-of-function of genes regulating the skin barrier. Another experiment showed how a particular "medicine" could help one of two dolls Rina and Mina, with the aim of communicating concepts related to inherited differences between individuals that could influence treatment responses. These interactions led by a doctor and a medical student resulted in lively interactive discussions with the children. Translation from Bengali to English was available. 99% of the participants reported they enjoyed the session and 88% reported an increase in awareness and knowledge of atopic disease and personalised medicine. The children found they learnt about asthma and allergy, and the concepts of genes and personalised medicine.

Exemplar quotes from children (translated from Bengali) are as follows:
"From today's discussion I learnt that each medicine may not work for everyone"
"how everyone's parts of the body are different due to genes and people look different."
"All medicines do not work on everyone."
"If the doctor gives a medicine, we should not use the medicine without understanding what it is."

The children expressed interest in understanding and reflecting on genetic research that could lead to tailored approaches to treatments. This work shows it is possible to engage with children regarding genetic research and hopefully will encourage biobank developers and genetic researchers in the Global South, including India, to ensure that the voices of marginalised communities, including children and women, exert significant impact on healthcare policy for precision medicine.

85: Genome-wide association analysis of infertility in men and women

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Infertility, defined as the inability to conceive after having tried for at least a year, affects approximately 15-20% of couples worldwide. Despite notable progress in identifying genetic determinants for infertility, few genome-wide association studies (GWASs) of infertility have been published.

Materials and methods: We performed a sex-stratified GWAS of infertility by combining summary statistics from six independent cohorts of European ancestry: MoBa and HUNT (Norway), NHSII (USA), ALSPAC (UK), and NFBC1966 and NFBC1986 (Finland). All cohorts included data from women (19,039 cases and 106,807 controls; total=125,846), while only MoBa, HUNT, and NFBC1966 included data from men (6,627 cases and 49,054 controls; total=55,681). We estimated SNP-based heritability using LD score regression, performed a phenome-wide association study (PheWAS) of 1402 ICD-based traits (aka "phecodes") in the UK Biobank to look for associated traits (p-value <3.6x10-5), and scrutinized the lead SNPs using the FUMA GWAS online platform.

Results: Despite low heritability in both sexes (around 1%), four loci were associated with infertility in women (p-value<5x10-8). The strongest signal was on chromosome 19p13.3, in 'RNA exonuclease 1 homolog' (REXO1) and 'KLF transcription factor 16' (KLF16). We also found associations in 'zinc finger DHHC-type palmitoyltransferase 2' (ZDHHC2; 8p22) and 'Wnt family member 4' (WNT4; 1p36.12). In men, we identified one locus in 'glutamate decarboxylase like 1' (GADL1; 3p24.1-p23). Our PheWAS analysis in women linked these findings to genital/uterine/vaginal wall prolapse, benign uterine neoplasms, uterine leiomyoma, and endometriosis. No associations were found in men.

Discussion: Despite the low SNP-based heritability observed in both sexes in our data, we still found significant genome-wide significant associations in several genes. REXO1 expression has been studied in various tissues, including those relevant to reproductive functions, but no specific role in either fertility or infertility has yet been identified. The same goes for KLF16 and ZDHHC2. However, our PheWAS analysis showed that the lead SNPs in REXO1, KLF16, WNT4 and ZDHHC2 were linked to several relevant infertility phecodes. Notably, WNT4 is recognized for its crucial role in the development of reproductive organs. Its deficiency can lead to conditions like Müllerian aplasia and hyperandrogenism in females. In males, WNT4 is involved in testicular development, and its knockout in experimental models leads to fertility defects like cryptorchidism (undescended testis) that can impede with male fertility. Finally, we did not find any evidence in the current literature directly linking GADL1 variants with fertility or infertility in men. GADL1 is known for its function in amino acid metabolism but has, thus far, not been implicated in reproductive health.

Conclusion: This comprehensive GWAS revealed significant genome-wide associations with more genes in women than men, suggesting distinct genetic influences on infertility across the sexes. However, it could also be that the smaller sample size for men yielded less statistical power to identify additional loci. The lead SNPs in several of the genes identified in the women's analysis were linked to several relevant infertility phenotypes. Except for WNT4, with known associations with fertility-related disorders, the other identified genes represent novel findings and warrant replication in other cohorts.

86: Optimized Library Preparation Kit and Workflow for Improving cfDNA Sequencing Sensitivity

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Next-Generation Sequencing (NGS) of cell-free DNA (cfDNA) has emerged as a promising strategy for early detection, diagnosis, and monitoring of cancer progression. In this process, cfDNA is extracted from a patient's blood and undergoes library preparation prior to NGS. The challenge with cfDNA library preparation is reliably capturing and converting all the fragmented DNA, especially when present in low concentrations within biological samples. Attaining low variant detection thresholds and variant calling confidence demands high-performance NGS libraries and targeted sequencing protocols.

Presented here is a workflow leveraging the Twist cfDNA Library Preparation Kit and an optimized target enrichment protocol to maximize the conversion of duplex, on-target, sequenceable sample molecules. It is demonstrated that by increasing target coverage we can increase detection sensitivity at low variant allele frequencies (VAF). In addition, this workflow improves detection of duplex-molecule families relative to comparable workflows due to more efficient four-point ligation and newly optimized target enrichment. It is also demonstrated that achieving improvements in complexity does not necessitate compromising data fidelity by introducing artifacts or losing uniformity. This improved conversion and sensitivity is applicable to as low as 1 ng input samples with both native cfDNA and synthetic cfDNA control.

87: Towards elimination of cervical cancer – increased use of biobanks enables rapid assessment of emerging biomarkers in screening

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

To achieve the WHO goal for global elimination of cervical cancer, Norway and other countries have implemented human papillomavirus (HPV)-based screening. Optimal follow-up of high risk (hr)-HPV positive women remains a challenge and molecular biomarkers which can increase screening accuracy are needed. DNA methylation analysis is a promising biomarker for separating between HPV-positive women with progressive potential disease and those with harmless infections. However, determining predictive accuracy of biomarkers in real-life is difficult, due to long follow-up required and ethics.

Our objective is to determine the optimal GynTect DNA methylation assay protocol for individual biobank sample types, assessing effects of storage duration and sample processing on assay performance and determine minimal amount input needed for optimal assay outcome.

Methods: The biobank: Residual cervical screening samples (LBC Thinprep) collected from consecutive 4242 participants who attended to National Cervical Cancer Screening Program in Norway in 2007-2013. Sample types: 1) Cells sedimented in Thinprep (Hologic); 2) cells resuspended in specimen transport medium (STM; QIAGEN) and 3) nucleic acid extracts Magna pure (Roche). The study: Samples from 60 participants were selected and anonymized (year of sample donation only known variable). Ethical approval was granted from Regional Ethics Committee of Southern Norway #2011/2341. For chemical treatment of the samples, prerequisite for the qPCR detection of DNA methylation markers, Bisulphite conversion was performed using Epitect Fast Bisulphite kit (QIAGEN, Hilden, Germany). For the bisulphite conversion, 40µl of sample input was used. For Thinprep biobank samples, initially 1ml sedimented biobank sample was centrifuged and resuspended in 50µl supernatant. To reduce input amount, assay performance was compared using 5x less (200µl samples centrifuged) and 25x less (40 µl direct input). GynTect DNA methylation analyses: The GynTect DNA methylation assay has been CE-IVD approved for LBC and STM samples. The samples which were bisulfite-treated as described above were used following the GynTect QPCR protocol provided by the manufacturer, using the cobas z480 Analyzer (Roche).

Results: Cervical screening samples stored long term at –80° displayed excellent GynTect DNA methylation assay performance. Optimal performance with 100% valid results (30 out of 30) was observed for cells stored in Thinprep. In comparison, assay performance was reduced for cells stored in STM (65% valid results, 26 of 40) and further for nucleic acid extracts (40% valid results, 16 of 40).

Conclusions: Stored cervical screening samples combined with known HPV genotype and clinical outcome (enabled by personal linkage with screening registries) are a resource for rapidly assessing diagnostic accuracy of emerging biomarkers. Data from retrospective cohort studies using biobanks will inform policy makers and speed up the process of implementations into the screening program. Studies to adapt protocols for individual biobanks is essential to ensure optimal assay performance and minimal sample use. Specifically for this pilot, we have demonstrated excellent assay performance with 100% valid GynTect results when using LBC cervical cells stored at – 80° in Thinprep. Fruitful collaborations between private sector and public institutions enable full exploitation of existing biobanks and emerging technologies.

89: Circulating RNAs prior to endometrial cancer diagnosis

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction:
The incidence of endometrial cancer (EC) has increased in the Nordic countries, and EC is now the most common gynaecological cancer in Norway. RNAs are influencing all cancer hallmarks and have potential as early diagnostic and prognostic cancer biomarkers.

Aim:
The study aimed to identify differentially abundant (DA) RNAs in females who subsequently were diagnosed with EC, compared to cancer free controls.

Material and methods:
We used a case-control design nested within the Janus Serum Bank. We analysed circulating RNA levels in samples collected 1-11 years prior to the diagnosis of EC for 316 cases and 316 cancer-free controls.

Results:
Our study (1) revealed DA microRNAs (miRNAs), isomiRs, and small nuclear RNAs (snRNAs) between EC cases and controls. The top EC DA miRNAs were miR-155-5p, miR-200b-3p, miR-589-5p, miR-151a-5p, miR-543, miR-485-5p, miR-625-3p, and miR-671-3p. The relationship between EC and RNAs was not constant, and it was influenced by body mass index (BMI), physical activity level, and smoking history. Our results also suggested a pattern of temporal variability in differential abundance of miRNAs preceding the diagnosis of EC.

Conclusion and next steps:
Circulating RNAs undergo alterations and demonstrate temporal changes prior to EC diagnosis. In the next steps, we plan to use machine learning (ML) approaches based on RNA features to predict EC case-control status. The dataset is high-dimensional, and highly valuable due to the fact that serum samples were obtained from individuals who subsequently developed cancer. We will additionally evaluate how inclusion of age at the time of sample collection and BMI and other variables contributes to performance of the models. Finally, we will evaluate feasibility of using ML methods to model time prior to EC diagnosis.

References:

1. Rostami S, Rounge TB, Pestarino L, Lyle R, Fortner RT, Haaland ØA, Lie RT, Wiklund F, Bjørge T, Langseth H. Differential levels of circulating RNAs prior to endometrial cancer diagnosis. Int J Cancer. 2024 May 11. doi: 10.1002/ijc.34951. Epub ahead of print. PMID: 38733362.

90: Enriching the hospital biobank collections with diagnostic leftover samples and returned data

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Auria Biobank has operated since 2014 and achieved the SFS-EN ISO 20387:2020 accreditation for human material biobanking in 2022 with the scope of liquid sample handling and distribution. Auria Biobank provides biological samples and related clinical data for research projects and has carried out over 300 biobank studies with academic researchers and pharma industry.
Finnish hospital biobanks store for example diagnostic FFPE samples and routinely collect one blood sample from each donor based on the biobank consent. In addition, biobanks can use the diagnostic excess samples after the diagnostic assays have been performed. Auria created a method for targeted collection of excess samples from the sample flow of clinical diagnostics at the Turku University Hospital and started to collect these in 2019. In four years, 2800 plasma, 3100 whole blood, 9900 serum and 800 cerebrospinal fluid samples have been collected from the daily sample flow of the hospital. Urine has been collected from 2500 cancer patients, and disease-specific blood collections have been established, such as hospitalized Covid-19 patients (1000 samples), patients with rheumatoid arthritis (500 samples) and patients treated with immune-checkpoint inhibitors (600 samples).
After finishing the biobank study, the researchers must return the raw data resulting from the analyses and assays to the biobank. The returning data is linked to the sample and thereby expands the sample-related data for future needs -the data produced from the sample can be utilized in further studies. The returned data is diverse and contains, for instance, genotypes, T-cell signatures, somatic variant data, and data for immunohistochemical stainings and redox-state alterations.

91: Chemokine CCL23 as a diagnostic and prognostic biomarker in systemic Mastocytosis

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Systemic mastocytosis (SM) is a rare bone marrow disease with a prevalence of around 10/100 000 inhabitants. Patients present either as indolent disease (ISM) with a normal life expectancy, or in around 10-15% of cases as an aggressive advanced phenotype (AdvSM) with bone marrow failure and a life expectancy of only 2-4 years. Over 90% of patients carry the same activating point mutation D817V in the KIT gene, rendering mast cells constitutively active and proliferating, causing symptoms from various organs including allergic symptoms, anaphylaxis, hives, itching, diarrhea, muscle and joint pain, and osteoporosis.

For SM diagnosis, a bone marrow biopsy is required. We and others have demonstrated a median 10-year delay between symptom onset and diagnosis likely due in large to the lack of readily available blood biomarkers. Currently, tryptase is the only available blood biomarker in the clinic, however 20-30% of SM patients do not have elevated tryptase levels and in addition, elevated tryptase levels are frequently seen in other conditions. Thus, there is an unmet need for novel, specific SM disease biomarkers to identify SM patients.

At Centre of Excelence for Mastocytosis at Karolinska University Hospital in Huddinge, Sweden, we have biobanked samples from almost all SM patients in the clinic of hematology and also healthy volounteers. Some of these samples were used for this study. A plasma proteomic screen was performed with the Proseek Immunooncology proteomics panel containing 92 inflammation- and cancer-related biomarkers at Olink Proteomics in Uppsala, Sweden. Plasma from 48 SM patients (39 ISM and 9 AdvSM) and 20 healthy controls (HC) were analysed. 5 cytokines (CCL19, CCL23, CXCL13, IL-10 and IL-12RB1) turned out to correlate with disease severity when comparing with the groups HC, ISM and AdvSM. These findings were then confirmed with ELISA for CCL19, CCL23, CXCL13, IL-10 and IL-6, that had commercially available ELISA kits. CCL23 was consistently increased in AdvSM compared to ISM, suggesting a potential correlation of CCL23 levels and disease severity.

To assess what cells produce the CCL23 chemokine, single-cell RNA seq was run for bone marrow MNCs from three ISM patients. They all showed distinct expression of CCL23 in the mast cell compartment and in the mast cell compartment only. IL-6 was also expressed mostly in mast cells, but in a limited fraction of the cells.

We are currently validating our findings in a large independent cohort of 100 SM patients and 100 population based, age matched controls, and planning for introduction of CCL23 into clinical routine for SM diagnostics and screening.

In conclusion, the cytokine CCL23 is predominantly produced by aberrant mutated mast cells in SM, and CCL23 levels correlate to SM disease severity. Our results suggest CCL23 as a potential diagnostic biomarker, and we are currently validating our findings in a large independent cohort to enable introduction into clinical routine.

92: KI Biobank - A Research-Integrated Biobank

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

KI Biobank at Karolinska Institutet is a research-integrated biobank uniquely capable of tailoring the processing of human samples to meet various research requirements. By adopting flexibility and adaptability in automation and data management, we offer processing of a wide range of samples and tube types, currently handling 80 sample types (e.g. plasma, saliva, viable cells) and 70 different tube types. KI Biobank supports scientists both within and outside of Karolinska Institutet on how to start a sample collection and on how the specimens should be collected. We advise researchers on ethical and legal requirements and help with establishing all necessary agreements under the Swedish Biobank Act. KI Biobank provide services such as design of study specific paper referrals, preparation of viable cells, automated sample handling (e.g. plasma- and serum aliquoting). In close collaboration with researchers, KI Biobank has during the past few years developed a pipeline suitable for collection of samples in precision cancer medicine (PCM) initiatives. Our PCM-services includes amongst others cfDNA/gDNA extraction and sample withdrawal on the same day, vital for real-time tumour profiling and treatment optimization. Upon sample withdrawals we can assist with reformatting and with ordering transportation of samples. In addition, KI Biobank has robust IT systems, ensuring full traceability of every sample and can provide each research study with access to sample balance reports and scanned referral data via KI Biobank´s FTP-server. Over the past 20 years, KI Biobank has grown and evolved, and today hosts over 8 million samples from nearly 800 000 consenting donors, participating in 230 active research studies with nearly 1 million samples withdrawn for scientific analyses.

94: The Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research, a longitudinal cohort biobank – A gold mine for population-based research.pos

PhD Marina Mola Caminal, PhD Anna-Karin Kolseth, Prof, PhD Karl Michaëlsson
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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

BACKGROUND: SIMPLER, the Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research started in 1987 and includes biological samples and data from 110,000 participants born 1914-1952 living in central Sweden - Uppsala, Västmanland and Örebro Regions.

METHODS: SIMPLER Biobank gathers health and lifestyle questionnaires with information updates on health status and drug use through 20 national patient and quality registries. Uppsala, Örebro, Chalmers and Karolinska Universities are responsible for maintaining the infrastructure and for providing national and international researchers with data and material sharing.

RESULTS: Repeat examinations in subcohorts include body composition by DXA (Lunar Prodigy), anthropometrics, grip strength, gait speed, timed up and go test, blood pressure, cognitive function test, clinical biochemistry, and additional lifestyle questionnaire before the examination. Collection of biological samples includes fasting whole blood, plasma, serum, buffy coat, fat biopsies, stool, urine, saliva, and DNA. SIMPLER has to this date genomics (N=50,000), targeted proteomics (N=13,500), untargeted metabolomics LC-MS (N=13,500) and microbiome data (N=7,000) with an ongoing enrichment of the omics data with new samples to be completed before 2028. The infrastructure has 2,500,000 person-years of observation with no loss to follow-up, and extensive high-quality phenotypic data with 4,500 variables per participant (excluding omics).

DISCUSSION: SIMPLER is a well-functioning and mature infrastructure enriched by questionnaire information and clinical examinations, omics data from a wide range of biological samples, additional large-scale collection of blood and stool samples, as well as database sharing costs and biobank operation. Combining all the data generated and hypothesis-driven studies it will be possible to refine precision medicine, translational studies, and drug target identification in order to help reducing the incidence of chronic and acute late onset diseases, easing their treatment and prognosis. SIMPLER provides a unique longitudinal cohort biobank for cutting-edge research in medicine.

95: Automated vs. Manual Ultra-Low Temperature Sample Storage: A Comparative Analysis of Space Efficiency, Power Consumption, Labor Efficiency, Running Costs, and Carbon Emissions

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Manual ultra-low temperature (ULT) freezers pose challenges for sample storage and retrieval. Manual freezers have low energy efficiency, and frequent door openings lead to temperature fluctuations and increased energy consumption as the freezer works harder to maintain the required temperature. This, coupled with the use of refrigerant gases, contributes to a high carbon footprint. Moreover, freezer capacity is not optimally utilized due to the need for access aisles and the constant rearrangement of samples, leading to wasted space. The manual retrieval process is time-consuming and labor-intensive, requiring researchers to physically locate and retrieve samples, further slowing down research workflows.

This model simulates the impact of replacing a large manual ULT freezer collection with an Azenta Life Sciences automated storage and retrieval system. By modeling time, power, space, carbon emissions, and running costs, we demonstrate a 77% reduction in electricity consumption and carbon emissions, an 83% reduction in floorspace, and a 40% reduction in labor hours.

Therefore, significant improvements can be obtained in operational efficiency, cost savings, and environmental sustainability by replacing manual sample storage with automation.

96: Inflammation-Related Protein Variants and Their Impact on Short-Term Functional Outcomes After Ischemic Stroke

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Objective: To determine whether genetic variants of inflammation-related proteins causally influence 3-month functional outcome (modified Rankin Scale, mRS) after ischemic stroke.

Background: Recovery from ischemic stroke varies significantly between individuals. The acute-phase inflammatory response is believed to play a critical role in this variability. While previous research has linked various inflammatory proteins (including interleukins, chemokines, surface molecules, and immune receptors) to stroke outcomes, their causal role remains unclear. This study aims to establish whether these proteins and genetic variants directly affect stroke recovery.

Methods: We studied 20 inflammation-related proteins previously associated with ischemic stroke outcome. Genetic variants associated with protein levels (within 100 kb of target gene and p-value $<5x10^{-8}$) were identified using data from the UK Biobank Pharma Proteomics Project (UKB-PPP). These variants were then aligned and matched with data from the Genetics of Ischemic Stroke Functional Outcome (GISCOME) study. To establish an independent set of genetic variants and ensure strong genetic instruments we applied LD pruning at a threshold of $R2<0.01$ and an F-statistic of $F>10$. Two-sample Mendelian randomization was performed for each protein to assess causality on GISCOME outcomes, both unadjusted and NIHSS-adjusted. Sensitivity analyses were conducted to ensure the robustness of the results.

Results: Variants for 17 of the 20 proteins were identified within UKB-PPP and GISCOME. Of these, CASP8, CD6, DNER, and TNFSF14 showed significant results in Mendelian randomization analyses, indicating a causal effect on stroke outcomes. More detailed results will be presented.

Conclusions: Our findings confirm the causal roles of CASP8, CD6, DNER, and TNFSF14 in short-term recovery after ischemic stroke, highlighting the importance of inflammation-related proteins in stroke outcome. These results warrant further investigation to enhance our understanding of stroke recovery mechanisms.

97: Helicobacter Pylori Infection and Alzheimer's Disease Risk: The Norwegian HUNT Cohort Study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Infections may play a role in dementia pathogenesis. Prior studies on the relationship between Helicobacter pylori (HP) infection and Alzheimer's disease (AD) have reported contradictory findings. We investigated whether HP infection is associated with increased risks of all-cause dementia, AD, and Cognitive Impairment (CI) among participants (n=1252) aged over 70 years in the Norwegian Trøndelag Health Study (HUNT). Serum HP antibody titers in blood samples, collected by the HUNT biobank during 1995-1997, were measured using enzyme immunoassays. A reference limit of more than 300 titers denoted serum HP-positive serological status. More than 20 years later, consensus-based cognitive assessments were made using standardized criteria. Logistic regression models explored associations between HP exposure and cognitive outcomes. Odds Ratios (ORs) and corresponding 95% Confidence Intervals (CIs) were reported for crude and models adjusted by baseline covariates including age, sex, education, BMI, marital status, and co-morbidities. Multiplicative interactions and stratifications for sex, age, education, C-reactive protein (CRP) levels, ApOE E4 carrier status, and marital status were conducted to investigate possible differences based on sex, education, CRP or APOE E4 carrier status. Sensitivity analyses included further adjustments by APOE carrier status or CRP levels in the adjusted models.

In this population-based cohort study, seropositivity (OR: 1.18, 95% CI: 0.76-1.80) or titers (OR: 1.02, 95% CI: 0.83-1.23) to HP were not substantially associated with AD risk. Similarly, HP seropositivity (OR: 0.93, CI: 0.64-1.33) or titers (OR: 0.96, CI: 0.80-1.14) were not associated with the risk of dementia or other measures of cognitive status, including CI and dementia-free survival. We did not observe strong statistical evidence for substantial differences based on sex, education, CRP, or APOE E4 carrier status. Further adjustments for CRP levels or APOE E4 carrier status did not strongly alter the effect size or magnitude of the associations between the HP exposure and cognitive outcomes.

Overall, our data did not show an association between HP and later dementia, including AD. Further investigation is needed to clarify the relationship between infections and neurodegenerative diseases.

98: Variation in the Causal Influence of Body Mass on Common Diseases Across a Lifetime

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background/Objectives: Obesity is a major risk factor for most non-communicable diseases. The burden of disease is substantially higher in the older part of the population, but how obesity affects disease risk at different ages is largely unknown. To quantify the causal impact of obesity over the lifespan, we introduce a new method – time-resolved Mendelian randomization – which estimates the time-dependent, cumulative effect of a sustained body mass index (BMI) on disease rates at high temporal resolution.

Methods: The method properly accounts for the time-dependence of the BMI instrument by operating on the time-gradient of the instrument effect on outcome and relies only on patient register data to estimate effects, using Aalen's additive hazard model. We applied the method to determine life-course effects on four common diseases in the UK Biobank, including type 2 diabetes, coronary artery disease, atrial fibrillation, and osteoarthritis.

Results: Substantial differences in life-course effects were observed between diseases. Time-series trends of the causal estimates for atrial fibrillation and osteoarthritis increased with age in a highly non-linear fashion. The effect of BMI on osteoarthritis reached significance more than 20 years earlier than the effect on atrial fibrillation. In comparison, a significant trough – a local minimum – in effect was found for coronary artery disease at around 60-70 years of age, in both sexes. A similar feature was also found for type 2 diabetes, but only in females. Besides osteoarthritis, obesity was a larger risk factor in males compared to females, at all ages above a critical time-point.

Conclusion: By resolving the causal effect of a lifelong exposure to high BMI in time, we can elucidate the temporal aetiology of obesity-related disease and find the appropriate age for introducing preventive interventions.

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Disclosure: All authors declare no conflicts of interest.

99: Challenges in Validating Small RNA Models for Lung Cancer Prediction

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Lung cancer (LC) remains one of the leading causes of cancer mortality worldwide, emphasizing the need for reliable predictive models to enhance early detection and treatment. This study aimed to validate XGBoost-based machine learning models for LC prediction using small RNA sequencing data that were derived from blood samples in the Janus Serum Bank (JSB) [1]. The validation was conducted in two cohorts: the Norwegian Women and Cancer Study (NOWAC) and the Trøndelag Health Study (HUNT). The original cohort, the JSB, included pre-diagnosis LC serum samples collected 1 to 10 years before diagnosis, limiting the selection of similar/matching validation cohorts available to replicate the original findings. Both NOWAC and HUNT include pre-diagnosis miRNA profiles from LC samples but they had distinct characteristics: NOWAC included only female participants (133 cases and 133 controls – with miRNA profiles up to 8 years prior to diagnosis), whilst HUNT (119 cases and 119 controls – with miRNA profiles up to 8 years prior to diagnosis) and JSB (542 cases and 519 controls – with small RNAs, including miRNA profiles up to 10 years prior to diagnosis) included both men and women. We attempted to validate the original results from the JSB despite known differences in sample size and sex of participants, as well as differences in laboratory protocols. To address differences in lab procedures, sample storage, and RNA sequencing platforms, we processed raw reads from all three datasets using the 'sncRNA-workflow' pipeline, followed by the same normalization steps. Due to data heterogeneity, and different software library versions, we trained a new XGBoost model on the new datasets using a subset of RNA features. These features were selected based on their importance in the original XGBoost model. We evaluated models including all RNA classes, as well as miRNAs and miscellaneous RNAs. Models including tRFs and isomiRs were excluded due to different RNA count distributions across the cohorts. Additionally, models were evaluated for different LC subgroups: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and an all-histologies group including NSCLC, SCLC, and other histologies.
Despite promising results in the JSB [1], the models failed to achieve satisfactory performance in the validation datasets. All the models achieved average AUC values around 0.50, with the exception of the SCLC models in the HUNT cohort, which achieved AUC values of 0.62 and 0.61 (Table 1). The analyses revealed significant differences in RNA expression profiles and counts between the cohorts, preventing the models from performing adequately and significantly impacting model transferability. Some degree of model overfitting to the JSB is also likely.
This study highlights the challenges of validating prediction models based on small RNA sequencing in cancer research, emphasizing the need for careful consideration of each cohort's specific details. Lessons learned for future studies include ensuring consistent sample selection and laboratory protocols across cohorts, enhancing feature selection stability and reducing overfitting in the discovery cohort. By sharing the difficulties we encountered, we hope to help other researchers design robust validation settings and improve reliability of predictive models.

100: Association of Plasma Brain-Derived Tau with Long-term Cognitive Outcome After Ischemic Stroke

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Background: Cognitive impairment is common after stroke, and young patients may live with this consequence for a long time. Predictors of cognitive outcomes after stroke represent a current gap of knowledge, and there is no predictive blood-based biomarker.

Objectives: To investigate acute-phase plasma levels of brain-derived tau (BD-tau) for association to long-term post-stroke cognitive outcome in working aged individuals.

Methods: This longitudinal study included acute ischemic stroke cases before 70 years of age without recurrent stroke during follow-up (n=204). Blood was drawn in the acute phase (median 4 days after index stroke). Plasma levels of BD-tau were analyzed using a novel ultrasensitive assay that selectively measures tau originating from the central nervous system. Brain infarcts were manually delineated from Magnetic Resonance Imaging, and volumes calculated. Cognitive outcome was assessed by the Barrow Neurological Institute Screen (BNIS) for Higher Cerebral Functions1, a test for screening cognitive function, at 7 years post-stroke. A test for association between BD-tau and cognitive outcome were investigated in linear regression models adjusted for age, diabetes mellitus, level of education and day of blood draw (Model 1); and additionally for stroke severity (Model 2).

Results: Median age at inclusion was 56 (48-61) years, 65% were males, and median BNIS score was 41 (IQR 37-45). Higher BD-tau were associated with lower BNIS score (standardized β per standard deviation change, Model 1: -0.24, $p<0.001$; Model 2: -1.3, $p=0.03$). BD-tau and infarct volume were higly correlated, and infarct volume showed similar associations to cognitive outcomes as BD-tau.

Conclusion: In conclusion, plasma BD-tau is a promising non-invasive and accessible biomarker for cognitive outcome that may provide similar predictive information as advanced neuroimaging, and future studies in larger cohorts are warranted.

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Reference

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101: Age-Related Changes in Adiposity and Disease Risks: a Longitudinal and Prospective Study in the UK Biobank

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Abstract
In this project, we assessed how accumulation and distribution of body fat changes with age, and determined adiposity-associated disease risks in middle to old age. For this purpose we utilized anthropometric and magnetic resonance imaging data from 36,831 participants of the UK Biobank, aged 45–82 years. Repeat measurements after an average of 2.7 years (SD=1.2 years) were available in up to 1688 participants which allowed for a longitudinal study on adiposity development across middle to old age. Linked public health records also allowed for prospective studies on adiposity trait-associated disease risk. Cox proportional hazard modelling was used to estimate baseline adiposity-associated hazard ratios for type 2 diabetes, hypertension, hyperlipidemia, cerebral infarction and myocardial infarction. We also utilized multi-variable Mendelian randomization to assess mediation of BMI-associated disease risks via adiposity traits.
Nine MRI-derived measurements of body- and organ composition were examined: visceral adipose tissue, abdominal subcutaneous adipose tissue, pancreas volume, pancreas fat fraction, liver volume, liver fat fraction, as well as anterior and posterior thigh muscle fat infiltration.
Cross-sectional and longitudinal data illustrate mean increases in several disease-associated adiposity traits across middle- to old age, such as: waist circumference, waist-to-hip ratio, visceral adiposity, as well as ectopic fat infiltration of the pancreas and thigh muscles. Despite these increases, BMI remained steady or even slightly decreased in old age.
Mediation analyses also highlight visceral adiposity and ectopic fat infiltration of the pancreas and liver as important causal risk factors for both type 2 diabetes and hyperlipidemia in female and male UK Biobank participants. Sex stratified analyses also suggest different pathogenic adiposity-associated effects in males and females, likely due to differential distribution of body fat and adipose-related metabolic activity between sexes.

103: A Wroclaw citizens health profile: First conclusions from PICTURE cohort studypos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background:
The main scope of the project "Population CohorT StUdy of Wroclaw CitizEns - PICTURE" is a comprehensive assessment of the health condition of Wroclaw inhabitants. Recruitment for the study was conducted among a group of 3750 children aged 7-14 together with parents or legal guardians, who were randomly selected from the PESEL database and stratified by age and gender. The second follow-up of the project is currently concluding.

Methods:
The PICTURE study was approved by the Bioethics Committee of the Medical University of Wrocław (opinion no. KB-667/2019). Prior to the study, informed consent was obtained from each participant for the study and biobanking of biological material in written form. All ethical aspects of the study comply with the Quality Standards for Polish Biobanks. 1250 children together with parent was planned to be examined during 2-year project period. A set of laboratory assays (morphology, glucose, HbA1C, creatinine, total cholesterol, HDL, LDL, TG, K, Na, TSH, D, ECG, spirometry, BP, anthropometric, ENT and audiological tests for each participant was conducted. Biobanking of biological material included the collection of whole blood, saliva, urine, and stool, along with accompanying data. Patients also filled up randomized questionnaires describing social status, nutrition lifestyle, physical activity, anthropometric parameters. WMU Biobank became the first in Poland to obtain the ISO 9001:2015 quality certificate in 2019 and the international accreditation ISO 20387:2018 in 2021. What confirms that each biological material and the associated data are of the highest quality.

Results:
During the baseline project 2465 Wroclaw citizens were biobanked, including 1229 adults and 1236 children. During the baseline of PICTURE project a total of 39695 samples were collected (serum, plasma, urine, stool, native saliva). So far, during the follow-up of the project, 1171 individuals have been examined, including 582 adults and 589 children. During the Follow - up of PICTURE project a total of 17565 samples were collected. The most frequently diagnosed medical condition in the studied cohort was allergies, identified in over 1/3 of all participants. Other conditions were diagnosed much less frequently. Doctors diagnosed musculoskeletal, gastrointestinal, thyroid, and heart diseases in 3-4% of children.

Conclusions:
PICTURE cohort study conducting will be a valuable contribution that allow city authorities for careful future preventive programs undertaken to protect the health of citizens. Thus, the improvement of their lifestyle will be obtained. It is also proof of the WMU Biobank social responsibility where the activities of promoting positive changes actions in the lifestyle of the region`s inhabitants is performed.

104: Safer pregnancies in rheumatic disease - applications of RNA-sequencing

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Objectives: Safer pregnancies for women with rheumatic disease. By combining the effort of the Norwegian National Network for Pregnancy and Rheumatic Diseases (NKSR) and their quality registry (RevNatus) with bioinformatic analyses of blood samples, linked to the clinical data, we aim to find differences in gene expression within different immune cell populations for Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and healthy pregnancies. By improving our understanding of individual responses to medication we hope to show that rheumatic patients can be stratified for better treatment during pregnancy based on the transcriptomic profile of their immune cells. This will improve life for patients and decrease the burden these disorders pose on the health care system, through personalized, precision medicine. Ineffective drugs and potentially severe side effects can thereby be avoided.

Methods: Samples from 84 SLE, RA, and healthy control pregnancies have been analysed with up to 7 timepoints per pregnancy. In total, over 335 blood samples were analysed through bulk RNA and 16 of these also through scRNA sequencing of PBMCs. We combined the bulk and single cell RNA analyses for cell-type estimation, validated by flow cytometry, before combining this in a cell-type adjusted analysis.

Results: We identified several points of dysregulation in samples from those with rheumatism with distinct RA, SLE and pregnancy signatures. The analyses showed that an altered cell type composition in blood separates SLE from RA and healthy controls; in contrast the RA profile appears to be driven by immune cell dysregulation as its gene expression generally is close to that seen in healthy controls. The methods used could not show epigenetic changes, nor the effect of medication, but an interferon signature was identified and distinct changes in signature genes for certain small cell populations were found for RA patients.

Further analyses: We will now continue this unique analysis with deconvolution of single-cell RNA analysis for 60 already sequenced PBMC samples and we aim to sequence an additional 98 PBMC samples that have already been collected and pre-processed and are ready for sequencing. Totalling over 150 PBMC samples analysed through single cell RNA sequencing and flow cytometry. We will analyse this expanded dataset to identify changes in cell type composition and cell type-specific gene expression related to disease and time as well as potential cell type-specific effects of medication. Including a cellular and an individual layer to the analysis also allows us create both an IFN signature per person, per cell type and analyse how the IFN levels changes from the first to the third trimester and into postpartum. This will give us new insight into the interplay between interferon, pregnancy, and rheumatic disease.

105: The Dutch BBMRI-node as part of the national health and life science data infrastructure Health-RI

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction – The Netherlands have been a member of BBMRI-ERIC since its foundation. Since 2021, BBMRI.nl has been integrated in Health-RI, the national health & life sciences data infrastructure. Here we describe the organization and activities of BBMRI.nl.
Results – Health-RI aims to build an integrated infrastructure for reuse of health & life sciences data for research, policy, and innovation. The Health-RI theme Biobanks & Collections, representing BBMRI.nl, facilitates that health data, biomaterials, and images from a wide range of collections, are collected, managed, stored, and made available in a harmonized manner. Key activities are the standardization of sample and data processing based on evidence and (inter)national alignment, the provision of support via services that enable their finding and sharing, and the distribution of knowledge towards the biobank community. A first national Biobanks & Collections Day was organized in 2023.
These goals are realized through collaboration between European Strategy Forum on Research Infrastructures (ESFRIs). Health-RI envisions to establish and manage an ESFRI-overarching service portfolio (a so-called “house of services”) to support health & life sciences researchers in the Netherlands, which is based on the developed infrastructural solutions from these individual ESFRIs, including BBMRI, ELIXIR, EATRIS, and EuroBioImaging.
Conclusions – The current organization of BBMRI.nl facilitates improved functioning as a national node of BBMRI-ERIC, increased alignment and collaboration between ESFRIs, and more added value for the Dutch community of researchers. We believe that the description of our organisation of the Dutch BBMRI node may be informative for other member states to explore possibilities.

106: DISRUPTOR Project: national concept of medicine 4.0 based on Regional Digital Medicine Centres pos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction: Medical Research Agency (MRA), the institution representing Poland in ECRIN has published the Government Plan for Development of Biomedical Sector 2022-2031 perspective. There, Regional Digital Medicine Centres (RDMCs) are one of the strategic initiative for MRA to propel AI integration in healthcare forward.
Materials: In 2022 a first national public programs for non-commercial clinical trials with obligatory biobanking were announced by MRA. All biobanks cooperating within clinical trials and RDMCs sponsored by MRA must follow by unified requirements published by BBMRI.pl representatives in Quality Standards for Polish Biobanks, recognized as a national guideline for biobanking.
Furthermore, in 2023 Digital Medicine Centres Network formation as strategic structures for databases connection and unificiation from universities, hospitals, biobanking facilities were pronounced. 18 RDMCs were chosen, and Wroclaw Medical University with the project DISRUPTOR: Digital Medicine: an Innovative approach for SuppoRt and UPgrade of the diagnosis and Therapy based On Research took 1st place. Two prominent clinical areas: rare diseases, cardiovascular diseases concentrated on heart failure, characterized by significant diversity in terms of the amount, nature and type of generated data including omics are in the project scope, supported by data from the pathomorphology, radiology and biobanking. Looking on the data science tools, analytic methods and algorhitms for DISRUPTOR project following smart solutions, including AI will be developed: 1) digital tools for prognostic, predictive and therapeutic AI algorithms based on clinical and omic data sets; 2) algorithms generating adverse effect alerts when prescribing multidrug combinations; 3) algorithms supporting patient monitoring; 4) algorithms supporting treatment process management.
Results: DISRUPTOR constitutes the first step towards the broad implementation of digital medicine within Biobank, Hospital and University. The aim is to standardize the acquisition and processing of health data for scientific and analytical purposes, ensure their highest quality and enable secure exchange of structured data, finally implementing innovative digital solutions.
Conclusions: RDMCs associated in DMCs Network will be prepared to serve real-time data analysis, support clinical trials and hospital care in the area of digital solutions, and retrospective analysis as well. The biobanking will be performed according to BBMRI.pl “Quality Standards for Polish Biobanks”.
Acknowledgement: Project „Digital Medicine: an Innovative approach for support and upgrade of the diagnosis and therapy based on research (RCMC "DISRUPTOR" at UMW)” was financed by the Medical Research Agency under contract no.2023/ABM/02/00003 – 00

107: The Data Warehouse Project – FAIR biodata from the population-based Janus Serum Bank

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Janus Serum Bank is a population-based biobank reserved for cancer research and is internationally unique in terms of size and number of cancer cases. The biobank consists of serum samples from 318,628 individuals collected between 1972 and 2004, mainly from persons undergoing routine health examination in different counties in Norway. The annual linkage with the Cancer Registry of Norway identified 118,405 cancer cases among the participants in the biobank as of December 2022. The pre-diagnosis collection of samples makes the biobank well-suited for studying early detection and risk biomarkers of cancer. Since the 1980s, the biological material has been actively used in research both nationally and internationally, resulting in return of biodata to the Cancer Registry of Norway, from over 100,000 samples. With the growing need for more comprehensive studies, it is crucial to follow the FAIR principles in research (Findable, Accessible, Interoperable, and Reusable). Currently, researchers can apply for the use of samples from Janus Serum Bank, however, access to previously generated biodata is not readily available for sharing and reuse. The raw and/or uncleaned biodata are stored in an unstructured manner within the Cancer Registry of Norway's sensitive platforms, and there is no tailored infrastructure in place for applying for or accessing these data. In the data warehouse project, we aim to harmonize and activate biodata from Janus Serum Bank to increase reuse from this valuable resource. To achieve FAIR biodata from the Janus Serum Bank, we will work with the following steps over the next years:

1. Mapping: Map projects, data files and variables and decide which metadata and data to include in the data warehouse.
2. Legal: Get legal clarifications regarding storing and sharing of biodata, cancer data and questionnaire data. A risk and vulnerability assessment will also be conducted.
3. Standardizing: Standardize and harmonize metadata, data files and variables.
4. Software: Acquire and utilize a software appropriate for data storage, data management and data sharing. We will also develop/participate in a local and national biobank explorer.

108: EU Horizon Europe: REACT – Respiratory host pathogen interaction – Setup of a prospective sample collection in Denmark

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction

The aim of the present work was to form a Danish prospective cohort by setting up a de novo collection of samples for downstream analysis in the Horizon Europe project REACT (101057129). The project focuses on obtaining in-depth immunological knowledge of virus-host interactions and the diversity in disease course and outcome in response to respiratory viral infection with influenza (INFL), SARS-CoV-2 (COVID), and respiratory syncytial virus (RSV). The analyses within REACT are also based on already collected materials from existing cohorts in four partner countries, and an upcoming prospective sample collection in Spain.

Method

In the Capital Region of Denmark, patients with Influenza Like Illness (ILI) are included in the project after informed consent. Patients will be recruited during two respiratory virus seasons, namely 2023/2024 and 2024/2025, from 1) general practitioners (GPs) already participating in the Danish Sentinel Surveillance System for respiratory infections (adults) and 2) from patients hospitalized at Rigshospitalet (RH) (adults and children 0-15 years (Y)).
We aim to include 1000 patients (including 250 hospitalized children) in Denmark. Biological material will be used for immunological analyses of plasma, B and T cells, and host genetic and viral analyses. Blood (in Li-Heparin and EDTA tubes) and airway material (oropharyngeal swab in UTM tubes or airway secretion) are collected daily and transported at room temperature (4°C for airway secretion material) within 4-8 hours after venipuncture with arranged transport to Statens Serum Institute for virus identification, and isolation and storage of PBMCs (peripheral blood mononuclear cells), plasma, whole blood, and virus.
From children, blood (2 ml/kg up to 20 ml) is only drawn if part of their planned treatment, and thus to ensure isolation of immune cells, Lung Resident Lymphocytes (LRL) are isolated from airway secretion samples when available. Adults included through their GP are invited for a follow-up blood sample 2-3 weeks after inclusion.
In addition, data is collected from a questionnaire (disease onset, symptoms and severity, comorbidity, and life style factors) and national registries (clinical variables, demography, and socioeconomic information).
The project is approved by the Danish Ethical Committee (H-22043067).

Results

During the first season, 53 patients (44 adults/9 children) were included. At RH, 24 hospitalized adults (INFL 6, COVID 14, RSV 5) were included (11 females(F)/14 males(M), range 26-80Y, median 66Y), and 9 children (all RSV) (6F/3M, 0.5-18 months, median 1.4 months). By two GPs, 19 adults with ILI (INFL 7, COVID 0, RSV 2, negative/other 10) were included (14F/5M, 24-76Y, median 37Y), of which 7 (5F/2M) had follow-up samples taken.

Discussion

We have established a scheme to collect, isolate, and store samples in a same-day procedure that is feasible for both clinicians and the receiving laboratory, and also suitable for multiple types of analyses. However, it has proven difficult to recruit GPs and to reach adequate patient enrollment. To increase patient inclusion in the upcoming season, of both patients consulting their GP and hospitalized patients, we expect to 1) include more GPs, 2) add an additional hospital, and 3) initiate sample collection earlier in the season.

109: Impact of hemolysis on circulating miRNA in fresh and biobanked Janus Serum Bank samples

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Hemolysis releases miRNAs into the serum and may also influence miRNA degradation processes and therefore alter circulating miRNA levels. Avoiding and controling for hemolysis is critical for miRNA measurements in clinical and research settings. We aim to investigate the impact of hemolysis on circulating miRNA expression levels.
Material and Methods: The impact of storage time and preprocessing of serum were assessed in 1074 serum samples from Janus Serum Bank representing the full range of biobank sampling timepoints. We also analyzed 12 fresh serum samples from volunteers, each with 6 concentrations of added blood lysate. Small RNA sequencing was used to determine miRNA levels and hemolysis was estimated by quantifying hemoglobin concentrations using a variation of the Beer-Lambert law at a wavelength of 414nm determined by a Nanodrop™ 8000 spectrophotometer.
Results: The blood lysis titration/controlled experiment showed that hemolysis changes the levels of more than 30 circulating miRNAs. Eight miRNAs were associated with hemolysis in the biobank serum samples, however, no association with storage time or preprocessing could be identified. Hsa-miR-451a and hsa-miR-486-5p were the most consistently altered miRNAs in these experiments.
Conclusion: Hemolysis has an overall impact on miRNA levels in serum samples and should be accounted for in analyses. In biobanked serum samples, hsa-miR-451a and hsa-miR-486-5p levels are indicators of hemolysis.

110: Professionalizing biobanking in Veterinary Medicine

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The Norwegian Veterinary Institute (NVI) analyses thousands of samples from fish, animals, food and the environment each year (176 000 samples in 2023). These are generated from national and international research projects, surveillance programs, outbreak investigations, national and international reference responsibilities and diagnostics. The samples are collected and analysed due to our mission in providing independent scientific support to the authorities and industry within animal health, animal welfare, zoonoses, antimicrobial resistance and food safety. The collections include isolates of bacteria, viruses, parasites and fungi, samples of blood, prepared aliquots of DNA, RNA and various tissues from fish, animals, food and the environment.

As a significant part of emerging infection diseases in humans have their origin from animals and the environment, these samples may be critical for surveillance and research preventing future human disease. A healthy and sustainable aqua-and agriculture is also crucial to ensure human food resources. NVI consider these biological collections as a non-renewable resource and a top-level decision has been taken to professionalize NVI`s biobanking. In 2018 the process of purchasing an -80 automated sample storage (ASS) for 3.5 million samples was initiated and in February 2024 final take-over of a Hamilton BiosL6 was fulfilled. A main aim is to establish FAIR (Findable, Accessible, Interoperable and Reusable) biological collections for future needs.

Professionalizing biobanking is a cross-disciplinary, continuous and complex manoeuvre. Sharing of experience installing an ASS with other institutions in agriculture, aquaculture and human health has been of significant interest. Some of the challenges and discussion points along the process line so far has been:

(1) Organizing and mapping of biological collections and respective metadata,
(2) Designing of ASS including both highly diverse legacy collections and unknown future samples,
(3) Choice of tubes and respective volume and sizes (complexity vs harmonization vs. functionality),
(4) Automation equipment in upstream/downstream laboratories,
(5) Technical building preparations for ASS installation,
(6) Service and maintenance needs,
(7) LIMS integration vs stand-alone solution,
(8) IT infrastructure & security,
(9) Decision making at all organisational levels,
(10) Funding,
(11) Coordination needs internally,
(12) Coordination externally with vendors,
(13) Prioritizing and defining scientific and economically value on individual collections
(14) Internal criteria/prioritization for storing samples.

Early in the process of purchasing a -80 storage, NVI had the pleasure of visiting reference institutions being ahead installing ASS, and received great help in preparing the tender and final implementation. We now hope to share our experience, and contribute to the excellent biobank networks established nationally and internationally. To our knowledge, NVI is the first veterinary institute in Europe installing a -80 ASS, and we consider this state of the art investment as an important part of the puzzle professionalising NVI`s biobank. Guided by the UN’s sustainable development goals, we

welcome collaboration and interest in our automated sample storage and sample collections, both for infrastructure and research purposes.

111: Should it stay or should it go? -Assessing the value of legacy collections

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Introduction: Biobank storage of human biological samples is costly for research projects, for institutions, and for the environment. Considerable resources are spent by research projects in planning and conducting sample collections, but the costs of long-term storage is handled differently depending on the project and the host institution. For the institutions, the costs of biobanking include investment and running costs for locations and equipment, as well as qualified staff. Further, the environmental cost of biobanking is an emerging topic, encompassing the use of harmful coolants, and power demands.
Principles for modern biobanking are maturing (1-3) and serve to ensure fitness for intended purpose and high value for research. In addition, the collections represent value in the societal and political domains. Legacy collections may be highly valuable, but several biobanks host sample collections that were either acquired before modern biobanking principles were established, or that have not applied these principles for various reasons. Hence, some sample collections may be resource demanding while having low overall value. The value of the collections also become relevant in the case of resource cuts or acute incidences requiring prioritization between collections.

Objective: Both limited resources and disaster preparedness require the critical evaluation of the value of legacy sample collections. The value for research and in the societal and political domains must be weighed against the costs of biobanking, to ensure sustainability and predictability. Here, we present our experience-based practice for value assessment of legacy collections.

Methods: The Core Facility for Biobanking at UiT hosts samples collected through population-based cohorts and other research projects, in a volume of approx. 75 ultra-freezers in 2023. The oldest samples date back to the 1970s. During the last 7 years, we have systematically evaluated the value of our legacy collections. The main aspects of the assessment include administrative and legal aspects, visual assessment of physical condition of the collection, and accessory data assessment. Collectively, these assessments constitute the basis for our recommendations to the owners of sample collections, in answering the question “Should it stay, or should it go?”

Results and discussion: As a result of our value assessment, we have recommended destruction of legacy collections corresponding to a volume of 15 ultra-freezers. This corresponds to approx.16% of the total sample volume in the biobank. The assessments have freed up space and resources to allow us to host several new sample collections. Consequently, the total value of the biobank has increased relative to the costs.
Our assessments have not considered the societal and political domains, which belongs at the administrative levels of the organization with overall strategic responsibilities. Nor does it include an analysis of the biochemical quality, which must be tailored to the specific use of the samples. Here, we present an experience-based approach, but a comprehensive gathering of practices and principles for value assessment of legacy collections is warranted and would help to unify and improve biobanking practices and optimize the use of biobanking resources.

113: Polygenic prediction of cardiorespiratory fitness: The HUNT study

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Cardiorespiratory fitness (CRF) is a major risk factor for cardiovascular morbidity and mortality, with heritability estimates ranging from 40% – 60%.
Aim: Develop and validate a polygenic score (PGS) for CRF (CRFPGS) and assess associations with cardiovascular disease (CVD).
Methods: Genetic effect estimates from a genome-wide association study on directly obtained CRF (n = 4 525) were used in a Bayesian regression framework to train multiple PGSs in an independent cohort from the UK Biobank (n = 65 674). The top performing score was identified and carried over to an independent testing cohort from the Trøndelag Health Study (n = 82 109) to test for associations with different CVD.
Results: The PGS-CRF association varied considerably as a function of model fit and phenotypic accuracy. There was a clinically meaningful difference in estimated CRF between the bottom and top decile of the CRFPGS in the target sample. Moreover, the CRFPGS demonstrated cardioprotective effects, with reduced risk for multiple CVD, including myocardial infarction, hypertension, heart failure, and hypertrophic cardiomyopathy. The CRFPGS appeared to be more suited to identify individuals with a genetic susceptibility to slightly higher lifelong levels of CRF, in part driven by lower BMI, rather than individuals with a potential for supraphysiological levels.
Conclusion: We developed the first PGS for CRF using gold standard phenotypes as the base data and three large, independent cohorts. A genetic susceptibility to a high CRF had a clinically meaningful impact on the phenotype and its associated disease risk. The lack of gold standard measurements of CRF in large, genotyped populations makes developing and validating a PGS challenging.

114: Bologna Neuroscience Biobank: towards a 2.0 model for multidisciplinary harmonized Neuroscience multi-omic researchpos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The preservation of biological samples has evolved from rudimentary private collections to sophisticated, well-organized biorepositories that serve as the cornerstone for scientific investigations. Biobanks play a pivotal role in advancing Neuroscience research, particularly in the context of rare neurological disorders.
The Neuroscience Biobank of Bologna (BNB), established in 2022, is a research hub dedicated to processing, storing, and distributing biological samples collected from patients diagnosed with neurogenetic, neuromuscular, and neurodegenerative disorders, along with associated clinical, diagnostic and imaging data. The BNB's core mission is to facilitate comprehensive research studies spanning basic, translational, and clinical applications towards the identification of novel biomarkers to optimize diagnosis accuracy and unravel pathogenetic mechanisms, ultimately advancing personalized medical approaches.
In 2024, the BNB embarked on a significant transition from a Biobanking 1.0 model, primarily focused on sample quantity, to a more advanced Biobanking 2.0 model, focused on data harmonization and biospecimen quality. This transition is essential to enhance the BNB's potential as a crossdisciplinary resource, enabling in-depth shared studies to improve the knowledge of rare neurological diseases. A standardized Quality Assurance system will be implemented to ensure the full traceability and integrity of biospecimens. The transition towards Biobanking 2.0 aims to raise the BNB to a state-of-the-art biobanking resource, embracing the seven associated neurobiology laboratories (Neuromuscular, Neuroimmunology, Neurogenomics, Neuropathology, Brain aging, Cell factory, Proteomics and Metabolomics) to provide high-quality integrated data.
The implementation of the advanced Biobanking 2.0 model, oriented towards integrated multi-omics research, will pave the way for significant interdisciplinary scientific projects in Neuroscience, enabling the application of data mining algorithms to identify predictive peripheral biomarkers for neurological diseases, ultimately contributing to improved patient care and treatment outcomes.

Keywords: Biobanking 2.0, Data Harmonization, Biospecimen Quality, Multi-Omics Analysis, Biomarkers, Rare Neurological Disorders, Neuroscience.

116: Best Practice for Norwegian Biobanks (Beste praksis for norske biobanker) - 3rd version

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Planning, establishing and operating biobanks demands a broad spectrum of tasks and knowledge in regulations and operation of biobanks. In addition, biobanking is constantly evolving and the biobanks are affected by internal and external changes. Therefore, guidance in biobanking is valuable for new and experienced biobankers.

There exist international best practices for biobanks, which provide guidance on managing and operating biobanks, e.g. the OECD Best Practices for Biological Resource Centers and ISBER Best Practices for Repositories. However, these documents are global and not always adapted to Norwegian regulations and needs. Therefore, best practices for Norwegian biobanks (Beste praksis for norske biobanker- BBP) has been developed to describe best practices for planning, managing and operating Norwegian human research biobanks.

The BBP is written in in Norwegian by biobankers belonging to the partners in Biobank Norway and is published at https://bbmri.no/. The first version of the document was published in 2014. During 2023 and 2024, BBP has been revised and a group of 28 biobankers has developed the third version. In addition to a general update and improvement of the document, the goal of the revision has been to adapt the document to the changes seen in biobanking and external factors affecting biobanks since the second version from 2019.

May 31st 2024 the third version of BBP was released. Among the changes and updates in the new version are:

- Updated links to relevant regulations and helpful information
- More references
- Less details in descriptions of topics where the biobank's organizations or institutes have guidelines, e.g. in HSE
- Sustainability thinking
- Clarification around genetic analyses and consent
- Description of lawful basis for processing of data associated to the biological material
- Data and sample sharing with third countries
- Guidelines for acquisition of a biobank information management system
- A part about risk management is added
- Description of report content when shipping samples

117: Establishing versatile urine biomarker analyses on a chemiluminescence platform at HUNT Biobank

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The HUNT Biobank has, in collaboration with the Kidney Research Group - Trondheim established a new analysis platform, MESO QuickPlex, from Meso Scale Diagnostics (MSD). MSD analyses are based on high-performance, electrochemiluminescence immunoassays and allow for measurements of up to 10 different biomarkers in the same well. The MESO QuickPlex is designed with focus on reliability, ease of use, and cost-effectiveness, and it requires very small sample volumes. The platform can measure >600 different well-documented biomarkers from various fields [1].
The MSD platform is based on assay kits and allows for multiple, simultaneous tests on a single sample. Several biological sample materials can be used, including serum, plasma, urine, spinal fluid, tears, tissue extracts, cell lysates. The analyses are based on an ELISA-like technique where, instead of a secondary antibody, a target molecule is labelled so that it emits light when an electrical current is sent through the well (electrochemiluminescence). This provides very good sensitivity and a wide measurement range, low background noise, simple sample processing, and fast reading [1].
The HUNT Study has collected data from questionnaires, clinical examinations, and biological material in four surveys: 1984–86 (HUNT1), 1995–97 (HUNT2), 2006–08 (HUNT3) and 2017–19 (HUNT4) [2,3]. The first project analyzed with the new platform focuses on chronic kidney disease biomarkers in urine (the Kidney Tubular Health Project). Analyses and protocols were planned together with the researchers. Fifteen different biomarkers organized, onto three different panels, have been analyzed in urine samples from 1800 HUNT3 subjects:
Panel 1:
Monocyte chemoattractant protein-1 (MCP-1), Interleukin-18 (IL-18) and Chitinase 3-like 1 (YKL-40) (9.6 %CV).
Panel 2:
Beta-2-microglobulin (B2M), Epidermal growth factor (EGF), Neutrophil gelatinase-associated lipocalin (NGAL), Uromodulin (UMOD), Osteopontin and Cystatin C (CyC) (6.3 %CV).
Panel 3:
Vascular endothelial growth factor (VEGF), Trefoil factor 3 (TFF3), Calbindin, Clusterin, Kidney injury molecule-1 (KIM-1) and Osteoactivin (16.2 %CV).

The platform has shown good analytical quality, and the wide analytical range omitted the need for repeated sample dilutions contributing to an efficient workflow. In general, the platform enables us to analyze a wide range of proteins, cytokines, chemokines, and metabolites in various biological samples. The ongoing research project serves as a first example using this analyses platform. Further details about the analytical workflow will be presented at the conference.

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118: Implementing digital droplet PCR analyses of methylated circulating tumor DNA (ct-DNA) at HUNT Biobank

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The HUNT Biobank is in progress of establishing a sample collection and analysis workflow targeting methylated ct-DNA. The background is an ongoing research project focusing on circulating tumor DNA (ct-DNA) in related to colorectal cancer (CRC). In a past project, CRC was detected by a panel of known methylated ct-DNA-markers in plasma samples from participants in the Trøndelag Health Study, the HUNT Study [1,2,3]. Blood samples from participants in the third survey, HUNT3 (2007-2009) were analysed in a test set and a validation set. Certain methylated ct-DNA were detected up to two years prior to the clinical diagnosis of CRC and could separate patients at high risk from those at low risk of recurrence and death. To follow up on this project, additional samples from HUNT and clinical samples collected in relation to the routine CRC screening at Levanger Hospital will target the promising biomarkers for CRC.
The planning of the sample collection and analytical procedures are in progress. To facilitate the analyses in this project, the analytical capacity and instrumentation has been established at the HUNT Biobank and initial tests of the pipelines are and will be conducted during 2024. These efforts represent an important collaboration between researchers at HUNT Research Centre, especially the HUNT Biobank, and Levanger hospital which will demonstrate exploration of validation of promising biomarkers and an example of a liquid biopsy test. Establishing these analyses requires a platform that can be expanded to e.g. absolute quantification of other RNA and DNA targets in addition to detecting and quantifying mutations and copy number variations. The analyses are based on digital droplet polymerase chain reaction (PCR) technology and will facilitate other projects with innovation potential. The digital droplet PCR (ddPCR) instrument is provided by BioRad along with a thermal cycler and droplet generator. The workflow for the current project also includes sample extraction using a QIAgen instrument, bisulphite conversion, and DNA quantification. More details about the analysis workflow will be presented at the conference.

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119: Ensuring quality and quantity of DNA in the sample collections at HUNT Biobankpos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The HUNT Study is a population-based study in Trøndelag containing data from 240,000 participants and biological materials from 120,000 participants [1,2]. Sample materials were collected in the following survey waves: The HUNT2 Survey (1995-97, n= 65,228), The HUNT3 Survey (2006-08, n= 50,800), and The HUNT4 Survey (2017-19, n=56,041) [2], and from those DNA has been extracted from buffy coat and blood clot samples since the early 2000s. Importantly, DNA samples from over 100,000 participants are stored in HUNT Biobank available for future research projects. To ensure optimal quality and quantity of DNA in the sample collections at the HUNT Biobank, the present study investigated the stability and potential long-term change in concentration and purity of DNA as well as investigated integrity of the DNA extracted using different methods.

Sample processing, extraction procedures, measurement methods, and storage time can influence DNA quality and quantity. A subset of extracted DNA samples from both buffy coats and blood clots were analyzed in 2022 to evaluate contemporary quality and quantity of the samples. DNA samples collected from the different HUNT surveys (both stock samples with high concentrations and diluted samples with lower concentrations) using different extraction methods were compared. DNA concentrations and purity were determined using spectrophotometers (NanoDrop and DropSense) and fluorometers (DTX and FilterMax). DNA Integrity Number (DIN) was determined using a TapeStation automated electrophoresis system.

Overall, concentrations of biobanked DNA samples had not changed considerably over time from point of extraction (2001-2020) to the reanalyzes in 2022. Still, differences in laboratory procedures and methods that had been altered over time influenced the interpretation of the results. Further, DNA purity and integrity were considered good for all samples. DIN was lower for HUNT4 samples likely due to the extraction method using magnetic beads are mechanically tougher on the DNA compared to the salt precipitation method previously used. In summary, DNA samples stored at the HUNT Biobank are of high quality, and hence optimal for research projects even after up to 20 years of storage. This project has generated knowledge concerning potential variations in quality and quantity of long-term stored DNA due to different extraction and measurement methods.

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120: The moderating role of educational attainment on genetic differences in 19 complex diseases in Finland and the United Kingdom

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Socioeconomic differences have been linked to health inequalities. Individuals with low educational attainment are at increased risk for cardiometabolic and mental health disorders. In contrast, high educational attainment has been associated with various forms of cancer, such as breast cancer and skin melanoma. Moreover, individuals with a higher polygenic burden are more likely to develop complex diseases. In this study, we aim to understand how differences in socioeconomic status and polygenic burden together give rise to health inequalities. We explored whether differences in educational attainment modify or mediate the polygenic risk for 19 complex diseases.

We integrated genomics, education, and health data from three studies (FinnGen, UK Biobank, and Generation Scotland) across 2 countries (Finland and the United Kingdom, N = 719,749). The participants were between 35 and 80 years of age at the time of entry into the study. We selected 19 complex diseases with a high burden in high-income countries, as measured by the Global Burden of Disease study, for which GWAS summary statistics were available to create polygenic scores (PGS). The calculation of SNP weights for estimating PGSs was done with MegaPRS. Educational attainment was classified according to the 1997 International Standard Classification of Education (ISCED) and categorized into low (ISCED ≤ 4) or high (ISCED ≥ 5) educational attainment. We performed Cox proportional hazard models with age at disease onset as the timescale to assess the effect of educational attainment, PGSs, and their interaction on complex disease incidence. Where possible, we performed a fixed-effect meta-analysis on the log hazard ratios (HRs) across the tested biobank studies.

In line with recent results from the INTERVENE consortium, we demonstrated that the PGSs were associated with increased disease incidence for all 19 complex diseases. Except for most cancers, including skin melanoma, prostate, breast, colorectal, and all cancers, individuals with high education have lower complex disease incidence. The effects of the PGSs and education were independent, though the association of high education and type 2 diabetes (T2D) was increased after adjustment for the PGS (unadjusted HR = 0.69 [95% CI 0.68,0.70], adjusted HR = 0.72 [0.71,0.74]). We observed higher PGS HRs (per SD change in PGS) for the low education group in 5 diseases (T2D, gout, rheumatoid arthritis, coronary heart disease, and major depression) and for the high education group in breast, prostate, and all cancers. For example, in T2D the PGS HRs per SD were 1.72 [1.70,1.73] in the low education group and 1.65 [1.63,1.67] in the high education group, and in breast cancer 1.57 [1.55,1.59] and 1.71 [1.67,1.74], respectively.

In summary, we observed heterogeneity in PGS effects across education groups suggesting educational attainment has a moderating role on genetic differences in at least 8 complex diseases. This may have an impact when incorporating genetic information into healthcare and is worth studying further to ensure equitable use of genetic information in healthcare.

121: canSERV – providing cutting edge cancer research services across Europepos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: canSERV is a € 15 Mio. project offering cutting-edge research services, enabling innovative R&D projects and fostering precision medicine for patients benefit. canSERV involves 18 leading organizations across Europe including Research Infrastructures, key organisations and oncology experts.
Objectives: canSERV's main objectives are: (i) offer at least 200 different unique Personalised Oncology relevant and valuable cutting-edge services; (ii) establish a single, unified, transnational access platform to request services and trainings; (iii) ensure oncology-related data provided will be fully compliant with FAIR principles and complement and synergise with other EU initiatives and (iv) ensure long-term sustainability beyond project duration. Furthermore, canSERV establishes the European Molecular Tumour Board Network (EMTBN) that is open for anyone to join. The EMTBN develops Molecular Tumour Board (MTB) consensus guidelines, an MTB outcome registry, and provides advice to scientists, clinicians, and MTBs.
Results: canSERV offers a series of open and challenge calls for access to services in the amount of ~ € 9 Mio. The calls are designed to support researchers to develop innovative research projects that explore cutting-edge methodologies and target critical gaps in cancer research and care by providing funding to resources/services. By encouraging the submission of collaborative proposals, canSERV aims to foster transnational cooperation, support a vibrant scientific community, and help to accelerate knowledge gain and transfer through defragmenting the European Research Area.
Conclusions: canSERV presents an unparalleled opportunity to accelerate cancer research, drive innovation, and improve patient outcomes. canSERV is granted by the EU Horizon programme under #101058620.

122: Genome-wide association studies in FinnGen and the UK Biobank highlight genes involved with both nociceptive and neuropathic pain

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Neuropathic pain is a category of pain that relates to damage of the somatosensory nerves, affecting over 7% of the general population. Symptoms generally include pain, numbness and muscle weakness in the distal limbs. Age is an important factor in the onset of neuropathic pain, along with manual occupation and social status. Neuropathic pain can occur in either the peripheral nervous system or the central nervous system, and is different from other categories of pain sensation, for example inflammatory, chronic, dysfunctional or nociceptive pain. Here, we wanted to study the genetics of neuropathic pain, its relations with sleep and psychiatric traits, and compare the results to more nociceptive forms of pain. We used genome-wide association studies (GWASs) to study the neuropathic pain subgroup of mono and polyneuropathies. Cases were defined as those diagnosed with ICD10 codes G56, G57, G58.0, G58.7, G58.8, G589, G59, G60, G61.1, G61.8, G61.9, G620, G62.1, G62.2, G62.8, G62.9 and G63. As cohorts we used FinnGen Release 12 (cases = 58,967, controls = 441,381) and the UK Biobank (cases = 23,472 controls = 462,878). Furthermore, we performed a meta-analysis (N=983,477) of SNPs shared between the cohorts. In the meta-analysis we detected a total of 8 genome-wide significant ($p < 5*10-8$) lead signals. These signals were located near the genes DIRC3, ARIH2, LINC02517, AC107223.1, HLA-DQB1, LINC02742, FTO and GAPDHP37. To fine-map the signal at the HLA-DQB1 locus, we performed a logistic regression model using the unrelated participants in FinnGen (cases = 34,002, controls = 262,595) and imputed HLA alleles. We detected significant (Bonferroni corrected p-value < 0.05) effects from HLA alleles B*08:01, C*07:01, DQA1*03:01, DQB1*03:02, DQB1*02:01. We performed genetic correlation between the FinnGen polyneuropathies data and sleep/psychiatric traits. The analysis demonstrated significant correlation between polyneuropathies and insomnia, short sleep duration, chronotype, anxiety, depression, neuroticism, restless legs syndrome. The correlation with these traits are similar to what has been reported for nociceptive pain. We also identified significant correlation between severe Covid-19 (hospitalization) and polyneuropathies. We performed Mendelian randomization (MR) which exhibited significant causal links between insomnia, anxiety/neuroticism, chronotype and multisite chronic pain as risk-factors for neuropathies. The MR results further indicated Neuropathies to be a significant risk-factor for anxiety/neuroticism. This study demonstrates the genetic background behind polyneuropathies and suggests significant comorbidities with sleep and psychiatric traits as well as severe infections. The results provide additional foundations for treatment strategies for neuropathic pain and for symptom screening in patients with comorbidities.

123: Premature Deaths, Incomplete Answers: Unmasking the Full Picture of Mortality in Danish Neonates

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Premature birth, birth before 37 completed weeks of gestation, is a public health problem and a major risk factor of neonatal mortality. Globally 35 % of neonatal deaths are caused by complications due to premature birth. Understanding the secondary (immediate and contributory) causes of neonatal death among premature babies is important for prioritising research efforts and postnatal care protocols. The present study evaluated the utility of reporting the secondary causes of neonatal death among premature babies in Denmark.

Methods: Using the Danish Personal Identification Numbers (CPR-numbers), the information from several national registers were linked together. We calculated the proportion of the primary (underlying) causes of neonatal death, supplemented with secondary causes of death in cases in which the primary cause of death was prematurity (livebirth before the completion of 37 weeks' gestation) recorded in the Cause of Death Register among liveborn, singleton, premature babies delivered in Denmark during 2013-2017 (n = 348 deaths). Medical diagnoses, procedures, and operations recorded in the Medical Birth Register and the National Patient Register were evaluated in cases in which the cause of death could not be determined beyond prematurity or unknown causes. Causes of Death were classified according to the "WHO application of International Classification of Disease (ICD-10) to deaths during the perinatal period" (ICD-PM).

Results: The number of neonatal deaths per 1000 live singleton premature births was 1.21 (95 % confidence interval: 1.09-1.35). After re-categorizing those deaths with a primary cause of death classified as "low weight and prematurity" (ICD-PM: N9) using the reported secondary causes of death, the most frequently listed causes of neonatal death among preterm babies were "respiratory and cardiovascular disorders" (ICD-PM: N7) (23.0 %). "ow birth weight and prematurity" remained the only recorded cause of death in 14.4 % of cases, whereas "neonatal death of unspecified causes" (ICD-PM: N11) was the reported cause of death in 7.8 % of cases. In 27.3 % of cases with N9 or N11 as the only reported cause of death, there is evidence in the Medical Birth Register and National Patient Register that the neonate received intensive care.

Conclusions: Death certificates, as recorded in the Cause of Death Register, in Denmark were inadequate for 22.1 % of neonatal deaths among premature babies. The process of reporting neonatal deaths in this population should be redesigned before the Cause of Death Register can be used to meaningfully monitor the pathological processes leading to these deaths.

124: Incidence trends and risk factors for Legg-Calve-Perthes disease: A Danish nationwide register-based study using publicly available data

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: Legg-Calvé-Perthes disease (LCPD) is a rare childhood hip disorder that may necessitate surgery, depending on its severity. Although the aetiology remains unclear, several risk factors, including ethnicity, geography, and certain medical conditions, have been identified. This study used publicly available data to investigate trends in the incidence of LCPD and identify potential risk factors.

Methods: This population-based case-control study used publicly available from the Danish Biobank Register, to identify 1,924,292 infants born between 1985 and 2016. We estimated age-specific incidence rates for four birth periods of equal duration (1985–1992, 1993–2000, 2001–2008, and 2009–2016) and investigated associations with perinatal conditions, congenital malformations, coagulation defects, autism spectrum disorders (ASD), and attention deficit hyperactivity disorder (ADHD).

Results: We identified 2,374 (81.6% male) diagnosed with LCPD at ages 2-12 years, corresponding to an overall incidence of 12.1 per 100,000 live births relative to the year of birth. The incidence of this condition declined across all four birth periods, irrespective of sex or age at diagnosis. Several perinatal conditions were associated with a higher risk of LCPD. Children with reported birth injuries (versus no reported injuries) exhibited the highest risk (RR: 7.48, 95% CI: 3.37, 16.63), followed by those with versus those without coagulation defects (RR: 4.77, 95% CI: 1.79, 12.69). Children diagnosed with syndromic (RR: 2.90, 95% CI: 2.08, 4.04) or non-syndromic major congenital malformations (RR: 1.86, 95% CI: 1.55, 2.23) (versus those with no malformation diagnosis) were also associated with higher LCPD risk. The development of LCPD was positively associated with several ASD and ADHD diagnoses. However, after adjusting for sex and birth period, the associations between ASD and ADHD were no longer significant.

Conclusion: Using publicly available data, we observed a declining incidence of LCPD in Denmark over a 32-year study period. Our findings also confirmed positive associations between LCPD and various perinatal conditions, coagulation defects, and congenital malformations, highlighting potential aetiological pathways for further investigation.

125: Is genetic liability to higher muscle strength a proxy for intrinsic capacity to resist age-related pathologies and mortality?

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background: High muscle strength has been associated with a lower risk for diseases and a longer lifespan. We hypothesized that muscle strength genotype may reflect individual's intrinsic capacity to resist age-related pathologies, as well as predict better survival after acute diseases and lower risk of premature mortality. These hypotheses, and whether the potential association of muscle strength genotype and mortality is influenced by long-term leisure time physical activity (PA), were tested in Finnish population-based datasets.
Methods: A polygenic score for hand grip strength (PGS HGS, ~1M SNPs) was constructed using Pan-UK Biobank (N=418,776) as a base data and SBayesR methodology. Association tests were conducted in the FinnGen cohort (n=342,443, age 40-108). For PGS HGS validation (n=429) and to test if physically active lifestyle can modify the association of PGS HGS and mortality (n=8,815, 53% women) we used the Finnish Twin Cohort (FTC). Disease diagnosis, death dates and causes (all-cause and cardiovascular (CVD)) were obtained from the national digital registers. PA was assessed three times during the years 1975-1990 using validated questionnaires. Linear and Cox regression models were utilized.
Results: PGS HGS explained 6.1% of the variation HGS and 5.4% in knee extension strength. In FinnGen, a higher PGS HGS predicted a lower body mass index (β = −0.112 kg/m2, P=1.69x10-11) in women but not in men (β=0.004 kg/m2, P=0.768). A higher PGS HGS reduced risk for selected cardiometabolic diseases 3–6%, chronic pulmonary diseases 6%, musculoskeletal and connective tissue diseases 2–10%, depression 5%, and vascular dementia 7%. A higher PGS HGS decreased risk for any dementia 6%, and for Alzheimer's disease 4% only in women. Participants with a higher PGS HGS had 4% decreased risk for cardiovascular and 3% for all-cause mortality. PGS HGS was not associated with better survival after adverse acute health events in FinnGen.
During the 16.9-year median follow-up time (143,723 person-years), 2896 deaths occurred, of which 1089 were due to CVD. We found a significant sex*PGS HGS interaction (P= 0.016) in all-cause mortality prediction, respectively, with higher PGS HGS associated with decreased mortality risk in men (all-cause HR 0.93 and CVD HR 0.88) Associations persisted after adjusting for PA. No PA*PGS HGS interactions were found. In FTC PGS HGS did not predict mortality in women.
Conclusion: The genotype that supports higher muscle strength protects against future health adversities but might not reflect recovery potential after severe adversity. Genotypes supporting low muscle strength may be associated with higher CVD mortality in men regardless of their adulthood physical activity.
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126: Environment, lifestyles and health – A recall pilot study in the Central Finland biobank

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Research into the genetic risk of common noncommunicable diseases has made considerable progress in recent years. Genome-wide risk scores can be used to estimate inherited disease risk and to consider this risk when developing personalized prevention and treatment strategies. In common diseases, lifestyle and environmental factors also have a significant impact on morbidity. Better identification of lifestyle and environment-related risks and a better understanding of their interactions could help prioritize risk factors at individual and population levels.
Cumulative lifestyle and environmental exposures (hereafter the exposome) can be calculated as individual risk sums. However, in contrast to genetic risk sums, the exposome risk sum varies with age and over time due to the different types of accumulation of various exposures. Collecting more comprehensive exposure data will enable better predictions of future morbidity, identification of the most important risk factors at specific age periods, and the development of efficient prevention strategies.
In this pilot study, we will conduct a recall survey in the Central Finland Biobank. Socioeconomic and lifestyle data will be collected using an electronic health, lifestyle, and environmental factors questionnaire. The collected data will be combined with participant data from the biobank register, including genetic risk scores, diseases and their risk factors, and blood metabolomics. Additionally, open-source information on environmental hazards and area-specific socioeconomics will be integrated. The project investigates the interactions of the exposome and genetics on human health.
Data collection for the recall study will be carried out on the Own Biobank platform using REDCap (Research Electronic Data Capture) software, a web-based application suitable for sensitive data collection. The lifestyle survey will include socioeconomic and lifestyle factors, sleep, stress, work-related exposures, and information about the personal living environment. Respondents will be motivated to complete the survey using an automatic personalized feedback function.
In the first phase, the recall study will be piloted among people diagnosed with type 2 diabetes who have genomic data available in the Central Finland Biobank (n=1,386). Only individuals who have given their consent for recalls in the Biobank consent form will be contacted. Respondents will be directed to log in to Own Biobank (fingenious.fi) to give consent for this new recall study. They will also consent for the data collected in this study to be archived in the biobank. Subsequently, participants will fill in an electronic questionnaire. The biobank will combine the questionnaire data with the biobank's register data and create a pseudonymized ID for research purposes, ensuring that researchers do not have access to personal identification data. Open-source national environmental data will be integrated into the dataset using postal codes.
The study will be conducted in cooperation with the University of Eastern Finland and the Finnish Biobank Cooperative. The project is designed to be scalable to a longitudinal study covering the whole of Finland. The pilot study has received the necessary permissions and will be completed in the fall of 2024. The larger project will be conducted from 2024 to 2028 with funding from the Research Council of Finland.
Project webpage: https://www.jyu.fi/en/projects/genetics-lifestyle-and-health-biobank-study-firi-life

127: Integrating Radiomic Features from MRI with Clinical Variables to Predict Prostate Cancer Recurrence.

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Prostate cancer is the second most common cancer among men worldwide [1]. Diagnosing this disease involves several steps, including prostate specific antigen (PSA) measurement, digital rectal examination DRE, multiparametric magnetic resonance imaging (mpMRI), and biopsy [3]. Despite progress in diagnostics, distinguishing between indolent and aggressive prostate cancer remains challenging [4]. Radiomics, which involves extracting quantitative data from medical images, shows promise in improving the accuracy of diagnosis, prognosis, and predictive modeling of prostate cancer [5]. The aim of the current study was to investigate the potential of radiomics to predict prostate cancer recurrence from mpMRI prior to robot assisted radical prostatectomy (RARP).In this study, mpMRI scans and clinical data from 395 patients diagnosed with prostate cancer were analyzed. Tumor probability maps were generated using PROVIZ, a radiomic-based machine learning detection and localization system developed within CIMORe at NTNU [7]. The analyzes were focused on the index lesions, selected based on the tumor probability score from PROVIZ, which indicates the likelihood of clinical significant prostate cancer being present. We used the PyRadiomics library to extract radiomic features from the index lesions using mpMRI [6]. We also considered clinical variables such as PSA levels, Gleason Grade Group (GGR), and age. To handle class imbalance, we used the Synthetic Minority Over-sampling Technique (SMOTE) [8], and selected top features with Recursive Feature Elimination (RFE) [9]. A logistic regression model, optimized with Optuna, predicted recurrence and was validated through cross-validation [10], [11], [12], Among the 395 patients, the average age was 65 years, and the average PSA was 10.29 ng/mL. Key radiomic features associated with recurrence are shown in Table 1. Our predictive model demonstrated robust performance, with key metrics such as accuracy, sensitivity, and ROC AUC confirming its reliability (Table 2). Statistically significant associations were found between recurrence and PSA levels, as well as Gleason Grade Group, and several other features (Table 1). Our findings suggest that certain radiomic features from MRI scans are strongly linked to prostate cancer recurrence. These results support previous research, highlighting the importance of texture features in predicting cancer prognosis [14]. Our predictive model, leveraging logistic regression and advanced feature selection methods, demonstrated significant accuracy and reliability. Notably, model performance was significantly improved when combining radiomic features with clinical variables, compared to models based on radiomics features and clinical variables separately. Specifically, the model trained on the combined dataset achieved an accuracy 0.82, a sensitivity of 0.78, a specificity of 0.87, and an AUC of 0.82. Our study's strength includes a large sample size and the use of advanced analytical methods, which enhance the robustness and reliability of our findings. This study underscores the potential of radiomics in predicting prostate cancer recurrence, suggesting that radiomic features could serve as non-invasive biomarkers for recurrence prediction, enhancing personalized treatment plans. The inclusion of clinical variables like PSA level and Gleason Grade Group significantly improved the model's predictive ability. Future research should aim for external validation and combine radiomics with other clinical data to further improve predictive models.

128: Danish Primary Care Trajectories

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Primary care data are a essential for early detection of symptoms and diseases since they cover events when a patient transitions from health to disease. Longitudinal disease trajectories have proven to be important for both understanding disease etiologies and early prediction of diseases. In this cohort study, we apply Danish primary care data (The Danish National Health Service Registry) to generate population-wide primary care trajectories spanning the years 1990-2021, covering 2.3 billion service events annotated across 75 primary care chapters. The data cover 8.1 million patients. We built service event trajectories by calculating significantly directed service event pairs and joined these in temporal order to form longer trajectories. The trajectories illustrate the most common paths in which patients progress in the primary care sector in Denmark. This complete mapping of primary care trajectories in Denmark comprises early markers and progression patterns of diseases in health-to-disease transition periods and beyond.

129: Age of autism diagnosis and family wellbeing: exploring the association and its confounding factors in the MoBa cohort.

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Early diagnosis is thought to be advantageous for children with autism and their families. An early diagnosis may offer more timely access to necessary support and services, as well as aid family members' understanding of autism and enable them to better meet the child's unique needs throughout their early development. Although an earlier age of diagnosis of autism is generally believed to be beneficial for the wellbeing of the autistic child, their parents, and their siblings, little research has explored this relationship. In this study, we investigate to what extent age at autism diagnosis is associated with the wellbeing of autistic children, their parents, and their siblings, while accounting for individual and family characteristics that may confound the relationship. To this end, we use questionnaire and genomic data from the Norwegian Mother, Father, and Child cohort study (MoBa; Magnus et al., 2016) and diagnostic information from the Norwegian Patient Registry (NPR). Our analytic sample (N = 1960) consisted of all children in MoBa who have an autism diagnosis recorded at least twice in the NPR. In MoBa, parents completed extensive questionnaires on lifestyle, health, and wellbeing during pregnancy, as well as at various stages during the child's development. Based on existing literature, we identified several factors with the potential to confound the relationship between age at diagnosis and family wellbeing, including maternal cohabitation status, household socioeconomic status, parental age at birth, and the child's intellectual functioning, motor functioning, language skills, and emotional and behavioural difficulties throughout the early developmental period. We also included a range of polygenic scores as covariates to account for some unmeasured aspects of confounding. Multiple linear regression models were used to estimate the extent to which age at autism diagnosis is related to individual family members' wellbeing (as indexed by measures of life satisfaction and symptoms of anxiety and depression) during childhood and adolescence, whilst correcting for confounders. Additionally, we performed multiple regressions with an interaction term between age of diagnosis and sex to investigate whether the effect of age of diagnosis is different for males than for females. The results of these analyses can help understand the complex relationship between the age at which autistic children are first diagnosed and family wellbeing. This is an important step in accurately characterising the benefits of of early and effective autism screening interventions.

130: Joint Effects of Recurrent Copy Number Variants and Polygenic Scores on the Risk of Psychiatric Disorders in iPSYCH2015 case-cohort

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Introduction: Previous genetic research has established the impact of both recurrent copy number variants (rCNVs) and common single nucleotide polymorphisms (SNPs) on the risk of psychiatric disorders. However, the joint effect of rCNVs and SNPs on the risk of these outcomes remains underexplored. In the large population-based study of the iPSYCH2015 case-cohort we sought to investigate how polygenic scores (PGS) indexed by the aggregated effect of SNPs modify the effect of rCNVs on the risk of major psychiatric disorders.

Methods: We used the iPSYCH2015 case-cohort comprising all cases (n=82,626) with hospital diagnoses of autism, ADHD, Schizophrenia spectrum disorder (SSD), major depressive disorder (MDD), and bipolar from a Danish birth cohort of individuals born between 1981 to 2008 and a random sample (n=41,346) nested within the same birth cohort. Samples were genotyped on the Infinium Psych Chip v1.0 and Illumina Global Screening Array v2.0. Phasing and imputation were performed on BEAGLE5. 54 rCNVs at 27 loci were called using PennCNV and all the putative calls processed by an in-house QCtreeCNV package were verified by visual inspection. External GWAS summary statistics were used for PGS computation, and the SNP effects were rescaled using SbayesR. PGSs were generated by PLINKv2 and normalized with respect to the mean PGS of the controls. Absolute risks of each diagnosis associated with rCNVs and PGSs were derived by fitting survival models, accounting for the inverse probability of sampling weights (IPS). To investigate the additive and interactive effects of rCNV and PGS, we fitted generalized linear models (GLMs) for each outcome. rCNVs were grouped using their LOEUF scores. PGS profiles were compared by performing Welch's t-test. All the analyses were restricted to Unrelated European subjects (n=96,599).

Results: Increased absolute risk associated with rCNV groups was confirmed overall for autism, ADHD, and SSD, but not for MDD. Individuals in the high PGS group exhibited an elevated absolute risk for the four disorders compared to the low PGS group. Moreover, an increase in PGS among rCNV carriers was associated with a higher absolute risk of psychiatric outcomes, with some variations, except for MDD. When examining the joint effect of rCNVs and PGS, we observed a significant additive effect on ADHD, ASD, and SSD. Comparison of psychiatric PGS profiles between rCNV carriers and non-carriers across cases and controls of each diagnosis did not reveal any significant differences when testing rCNV carriers categorized in LOEUF groups, although among carriers of individual rCNVs, ADHD cases with a 17q12-deletion had a significantly higher PGS compared to non-carriers. rCNVs×PGS analyses did not demonstrate any significant multiplicative interactions between the two genetic factors on the risk of psychiatric outcomes, whether considering rCNVs individually or in an aggregated manner, except for a nominally significant interaction between16p13.11duplication and ADHD-PGS in ADHD.

Discussion: The simultaneous assessment of recurrent copy number variants and common variants concerning the associated risk of ascertained psychiatric outcomes in the population-based iPSYCH2015 study provides insight into the implementation of genetic risk profiling in healthcare, thus enhancing precision medicine.

131: Mitochondrial DNA Haplogroup Variation and Psychiatric Disease

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background
Psychiatric disorders are complex, polygenic conditions with overlapping genetic architectures comprising hundreds of genes. Despite frequent findings of perturbed mitochondrial function, the role of mitochondrial DNA (mtDNA) variation in psychiatric diseases has not been resolved.
Objective
Examine the association between psychiatric disease and mtDNA haplogroups, sets of mtDNA polymorphisms with varying functional properties.
Design
mtDNA haplotyping and nucleogenomic ancestry were determined for the Danish iPSYCH cohort using genome-wide SNP analysis on the Illumina PsychChip v1.0 (Psychiatric Genetic Consortium). DNA was extracted from dried blood spots from the Danish National Neonatal Screening biobank. Associations between mtDNA haplogroups and clinical, demographic information from Danish health registries were investigated.
Setting
Population-and register-based case-cohort study using data from Danish electronic registries. Samples were collected from 1981- 2005.
Participants
A total of 66,501 Danish individuals were included in the study: 3,023 with schizophrenia (SCZ), 17,665 with affective disorder (AD), 1,954 with bipolar disorder (BD), 11,576 with autism spectrum disorder (ASD) and 9,985 with attention deficit hyperactivity disorder (ADHD). Additionally, 22,662 individuals served as random controls. Passive consent was employed, enabling unbiased sampling based solely on register data.
Main Outcomes and Measures
Odds-ratios, corrected for nucleogenomic ancestry and known risk factors, of mtDNA haplogroups as predictors of risk for overall psychiatric disease or specific psychiatric disorders.
Results
Haplogroup J was associated with overall psychiatric disease, aOR 1.10 (95%-CI, 1.03-1.16, p = 0.0014). Significant associations were found with AD, BD and SCZ, with adjusted odds-ratios from 1.11 – 1.26, and p-values 0.007 – 0.008. Haplogroup A was associated with SCZ, aOR 2.8 (95% CI, 1.4 – 5.3, p = 0.0022), and haplogroup D with ADHD, aOR 2.8 (95%-CI, 1.4 – 5.9, p = 0.005), within the macrohaplogroups N and M, respectively. For haplogroups J, and D, the associations were independent of genomic ancestry, whereas haplogroup A defined a nucleogenomic signature associated with SCZ.
Conclusions and Relevance
Variation in mtDNA is associated with psychiatric disease, either directly through effect on mitochondrial function, or indirectly as markers of nuclear genomic ancestry or environmental exposures. MtDNA haplotyping is a potential tool in precision psychiatry.

Maintaining Sample Integrity During Repeated Freeze/Thaw Cycles

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The frequent requirement to retrieve and re-store biological materials or newly synthesized compounds in -80°C freezers often necessitates repeated freeze/thaw cycles, raising concerns about the potential degradation of sample integrity over time. This study aims to evaluate whether samples stored in high-quality screw-cap sample tubes rated for -80°C storage experience any degradation due to long-term storage or repeated freeze/thaw cycling.

The study employed uniquely designed sample storage tubes of varying volumes, uniformly sealed, with dual threaded cap design, and different treatment types. At predetermined intervals ranging from two weeks to three years, the tubes were removed from -80°C storage, thawed to room temperature, weighed, and visually inspected for any damage such as cracking or grazing. The assessment focused on measuring any changes in sample storage volume, potential tube damage, and the efficacy of the dual-threaded cap design in preventing leakage and evaporation.

Across all tube types and conditions tested, findings indicated minimal weight loss and no physical damage. The consistent performance across different volumes and treatment types highlights the importance of robust cap design and material selection. The double-start thread and compression seal design effectively prevented cross-threading and over-tightening, contributing to the tubes' durability. Additionally, the use of a polypropylene polymer with low levels of extractables and leachables for both the cap and tube body minimized potential leakage due to differential expansion and contraction, without compromising the sample.

The study confirms that high-quality screw-cap tubes, when properly capped, maintain high sample integrity and exhibit minimal weight loss during long-term -80°C storage and repeated freeze/thaw cycles. These findings demonstrate the suitability of these tubes for biobanking and compound management applications that require multiple sample accesses over time, underscoring the critical role of cap design and material selection in ensuring reliable sample preservation.

133: Detection of structural brain aberrations in patients with dementia using explainable artificial intelligencepos

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Dementia is a clinical condition incurring memory loss, cognitive impairments, and behavioural changes in those afflicted. The biological manifestation of dementia in the brain is heterogeneous, leading to individualized cognitive and functional deficits. Providing precise, personalized characterization of the disease at an early stage could widen the window for early interventions, alleviate uncertainty for patients and their caregivers, and, potentially, guide accurate therapeutic interventions. While earlier studies on explainable artificial intelligence (XAI) in dementia have shown its usefulness to align the decision processes of AI and human experts, no one has investigated whether such techniques can be used to personalize diagnosis and prognosis. Here, we trained three-dimensional convolutional neural nets (CNNs) on structural brain magnetic resonance images (MRIs) to differentiate between patients with dementia and healthy controls. In a diverse, multi-site sample, our best classifiers achieved satisfactory performance with an out-of-sample AUC of 0.91 (accuracy=84.95%) in hold-out test data. Next, we implemented layerwise relevance propagation, a technique from XAI for explaining individual model decisions, on top of the CNNs. Together, these components composed a computational pipeline procuring both predictions, denoting whether a given brain MRI resembled that of a dementia patient, and individual-level explanations in the form of heatmaps, highlighting brain regions underlying the prediction. To validate the maps, we compared the regions they highlighted with a statistical reference map containing known pathological regions from a meta-analysis of 394 experiments from 124 studies on dementia patients. Overall, the heatmaps generated by our pipeline showed substantial overlap with the reference map, indicating that the CNNs learned to recognize dementia by looking at brain regions known to contain pathology. Finally, we applied our pipeline to a longitudinal cohort of patients with mild cognitive impairment (MCI) to test its efficacy for prognosis and personalization. For prognosis, predicting whether MCI patients convert to dementia within five years, our best-performing model yielded an AUC of 0.82 (accuracy=83.45%). For personalization, we observed significant associations between facets of the heatmaps and diverse cognitive domains from neuropsychological testing batteries, indicating the ability of our pipeline to relate biological and clinical heterogeneity. Overall, our results demonstrate the potential of XAI to characterize pathology in individual patients with a resolution beyond what can be achieved by traditional predictive modelling.

134: Branched-chain organic acidurias/acidemias in Denmark from 1996 – 2020: A nation-wide register-based case-cohort study of trends in birth prevalence, pregnancy complications and consequences of newborn screening

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background
The branched chain amino acids (BCAs) leucine, isoleucine, and valine are metabolized to acetyl- and/or propionyl-CoA that enter the Krebs cycle. Genetic defects in the enzymes of these pathways give rise to very rare inborn errors of metabolism, branched-chain amino acidurias/acidemias (BCAAs). The most frequently diagnosed are Maple syrup urine disease (MSUD), Isovaleric acidemia (IVA), Methylmalonic aciduria (MMA) and Propionic acidemia (PA). All the diseases exhibit an autosomal recessive pattern of inheritance. Early diagnosis and initiation of treatment by a specialist team is important, as it reduces mortality and morbidity. However, the scarcity of the BCAAs makes it difficult to establish birth prevalence, comorbidities and effect of neonatal screening. In Denmark, MSUD, MMA and PA have been part of the extended New Born Screening (eNBS) since 2002, whereas IVA was added to the eNBS in 2012. We used the recently designed Danish National Biobank platform (www.biobanks.dk) to study the development of birth prevalence, and antenatal comorbidities of the BCAAs MSUD, IVA, MMA, and PA, among Danish children born – and subject to NBS - over the 25-year period 1996 – 2020. Finally, we assessed the performance of eNBS for BCAAs.

Results
Birth prevalence
In the study period 1,513,558 liveborn children (49 % women) were included in the cohort. The observation period of patients varied from 3 to 25 years, as the NPR was assessed in Jan 2024. A total of 52 cases of BCAAs were identified. This corresponds to a total birth prevalence of 3.44 x 10-5. No temporal trend in birth prevalence was noted. Individual disease birth prevalences were 1.26 x 10-5 (0.69 – 1.82 x 10-5) for MSUD, 0.79 x 10-5 (0.34 – 1.24 x 10-5) for IVA and 1.39 x 10-5 (0.79 – 1.98 x 10-5) for MMA/PA.

Course of pregnancy
The number of BCAAs born premature or with a low birth weight (1500g – 2499 g) was < 5, corresponding to a proportion < 10 %, and no children born with extreme or very low birth weight, as well as immaturity, were noted. Likewise, < 5 were postmature. Five patients were small for gestational age.

Performance of eNBS
The performance of screening is assessed by calculating the proportion of BCAAs identified in the first year of life and comparing the periods, 1996 – 2002, prior to introduction of eNBS, 2003 – 2008, a period of voluntary informed consent-based eNBS, with an acceptance rate going from 65 % to 85 %, and the following period, where eNBS was part of the routine NBS. For IVA, it was only introduced into the eNBS in December 2012. The proportion of BCAAs identified within first year of life was 31 % pre-screening, 50 % in the voluntary eNBS period, to reach 96 % during routine eNBS.

135: Full-exome analysis of xanthine dehydrogenase gene: possible implications for tuberculosis pharmacogenetic studies.

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Tuberculosis (TB) is a serious contagious infection disease that continues to pose a significant public health challenge worldwide. Standard chemotherapy for drug-susceptible TB cases includes isoniazid, rifampicin, ethambutol and pyrazinamide (PZA). Inter-individual variability in pharmacokinetic (PK) parameters and drug plasma levels may affect treatment responses and occurrence of adverse drug reactions. PZA plays a crucial role in anti-TB therapy because of its sterilizing properties; it is also being considered as a companion drug in novel anti-TB regimens. However, PZA-induced hepatotoxicity, which is reported in about 15% of the patients, is a notable concern. The main stages of PZA metabolism involve a microsomal deamidase which induces PA formation, followed by xanthine dehydrogenase (XDH), which induces 5-OH-pyrazinoic acid (5-OH-PA) formation. Another metabolite is 5-hydroxy-pyrazinamide (5-OH-PZA) which results from direct action of XDH on PZA, followed by amidase-mediated hydrolysis to form 5-OH-PA. The aim of this study was to develop NGS-based sequencing protocol for full-exome XDH gene analysis and to evaluate the role of XDH gene heterogeneity in variability of PK parameters of PZA. The study cohort included 43 patients with TB admitted to the Riga East University Hospital, Centre of Tuberculosis and Lung Diseases. Blood plasma concentrations of PZA, PA, 5-OH-PZA and 5-OH-PA were measured using LC-MS/MS method in samples collected pre-dose (0h), 2h and 6h post-dose. Sequences of all 37 exons of XDH gene were obtained by using NGS-based protocol developed to amplify exons with intron flanks and UTR regions. Detected SNPs were annotated and identified using the wANNOVAR online-based tool and the NCBI dbSNP database.
Remarkable inter-patient variability in PZA exposure (AUC0–6) was observed. At 2h time point the average PZA blood level was 39.81 mg/L; 34.9% patients had PZA blood level below the defined therapeutic range (<35 mg/L). At 2h and/or 6h time points 16.3% patients had PZA blood level above the defined therapeutic range (>50 mg/L); hepatotoxicity was observed in all these patients with one exception; also, in one patient with hepatotoxicity PZA blood level was within the therapeutic range. Overall, 20 XDH gene SNVs were detected in DNA samples of the patients, including exonic and UTR polymorphisms, and some rare variants. Further analysis indicated that metabolic ratio AUC0-6h 5-OH-PZA/AUC0-6h PZA was significantly associated with patients' age, biological sex, creatinine level, CRP, and hepatotoxicity. In addition, statistically significant associations were observed for two SNVs of XDH gene: rs6752058 (this SNV was in LD with rs6710015) and rs2295475.
In conclusions, the obtained results indicated that XDH gene variants, along with several patient-related factors, could have an impact on changes in PZA metabolic parameters. Remarkable inter-patient variability in PZA exposure and PK parameters deserves additional studies. Developed protocol for XDH gene analysis can be applied in sub-population level association studies to determine whether specific genetic variants or variant combinations from multiple regions of the XDH gene are of clinical significance.

136: Missense variant in GPR101 in X-chromosome predisposes to sleep fragmentation (in sex specific fashion)

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background/objectives

Studies on habitual sleep duration and sleep disorders show large sex differences so that women sleep approximately 30 minutes more than men. We have earlier described genome-wide association results with sleep, chronotype and fatigue but the role of variants in the X chromosome and their possible sex-specific effect have remained unexplored in these earlier studies.

Methods

Using FinnGen R10 data (N=412,181 individuals) and UK Biobank for self-reported (N = 420,000) and activity derived sleep measures (N = 90,000), we examined the role of variants in the X chromosome.

Results

We found an association between a missense variant (rs1190736, allele frequency 50%) exonic of GPR101 and increased use of sleep medications. Analysis of rs1190736 with Polyphen suggested the variant to be damaging and accordingly, a follow-up analysis in objective sleep measurement data using activity watches showed a significant association with sleep fragmentation ($P < 5e-8$). The effect size of the variant was larger for females than males. The GPR101 gene encodes a G protein-coupled receptor known as GPR101.

Conclusion

Our findings imply a possible role of GPR101 in the regulation of sleep. Lacking a known ligand, the orphan GPR101 receptor has been found in previous analyses to be linked to several diseases and health-associated behaviours; these include a causative role in X-linked acrogigantism and acromegaly. Our findings may suggest a role of GPR101 in sleep consolidation.

137: Quantitative estimates of microbiome heritability and their implications

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

The microbiome mediates a variety of host traits that are consequential for health including immune function, digestion, and disease risk. As a result, there is great interest in understanding how microbiomes contribute to trait variation in their hosts and whether microbiomes could be a target for medical therapeutics. However, one challenge for implementing such approaches is our limited understanding of the mechanisms of microbiome transmission and to what extent microbiomes are heritable. The existence of heritable microbiome attributes has been controversial, especially for plants and vertebrates where strict vertical transmission of microbes is rarely documented. As a result, microbiome scientists have attempted to estimate the heritability of a variety of microbiome attributes. Despite decades of interest in this topic, we show that published estimates are limited to only a few vertebrate and plant hosts. However, for these species, significant heritability of microbiome attributes has been frequently reported. This suggests that microbiomes could evolve in response to host-level selection, but that studies across a much wider range of hosts are necessary before general conclusions can be made. We suggest that future studies focus on standardizing measurements of heritability, expanding the microbiome traits studied to include microbiome functional attributes, and investigate the role of the environment in contributing to heritable microbiome variation. Understanding the role of the environment as well as genetics in microbiome composition could be vital for our ability to implement microbiome therapeutics in the clinic. Results from such research could have important implications for the use of microbiomes in conservation, agriculture, and precision medicine.

138: Applications of COSGAP: COntainerized Statistical Genetics Analysis Pipelines

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Replicable and reproducible analysis and modeling of person-sensitive, large-scale digital data for prediction poses multiple challenges. The data, such as diagnostic, genetic, and imaging data, may reside in different secure hospitals, biobanks, and high-performance computing (HPC) facilities within the country, but also across borders. In practice the data may not be transferred due to legislation, necessitating federated learning and analysis approaches [1] and downstream meta-analyses as illustrated in Fig. 1. Ensuring a consistent set of tools, codes, required reference datasets, and analysis pipelines across each site is thus another challenge. Containerization of necessary tools for distribution is a reliable, cross-platform technology readily supported on personal computers, cloud infrastructures, and most HPC environments. In Akdeniz et al. [2], we introduced "COSGAP" – COntainerized Statistical Genetics Analysis Pipelines (https://cosgap.readthedocs.io; https://github.com/comorment/containers), an ongoing project that provides a comprehensive set of tools for statistical genetic analyses and prediction, e.g., genome-wide association, polygenic scoring, LD score regression, Gaussian Mixture Models and gene-set analysis, as well as prepackaged Python/Jupyter and R/Rstudio environments for general-purpose data analytics and modeling that are freely available and released under open-source agreements. The corresponding software containers are distributed on Docker and Singularity formats that are well supported by different platforms. Here, we aim to describe COSGAP, novel developments, and demonstrate its application to real-world Norwegian cohort data.

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139: HLA imputation in the Norwegian Mother, Father, and Child Cohort

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The HLA locus encodes cell surface molecules vital to the immune system, by presenting antigens, both self and foreign, to T cells. It is a complicated genetic region of extremely high variability and longe-range LD, which is poorly captured by most high-throughput genetic variation ascertainment methods. Specialized HLA imputation methods are required to capture the multilevel allele structure from genotyping arrays and NGS data. Knowledge of HLA alleles is important for tissue typing, and HLA alleles are among the most strongly associated of genetic variants in a range of diseases, especially autoimmune ones. However, HLA imputation can be cumbersome, uses some non-standard considerations, and it is usually recommended to run at least two different imputation softwares to account for biases. Here, we use HIBAG and CookHLA to impute HLA alleles of Norwegian Mother, Father, and Child Cohort with the aim of creating a reusable dataset for the use of the scientific community interested in studying immune-mediated conditions in this unique resource.
We present results from near-complete and pilot runs (210k individuals for HIBAG, 20k for CookHLA), and examine their accuracy and biases.

140: Low polygenic risk score for autoimmune Addison's disease identifies misdiagnosed cases of monogenic primary adrenal insufficiency

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Background:
Primary adrenal insufficiency (PAI) is sometimes misdiagnosed as autoimmune Addison's disease (AAD), affecting clinical management and genetic counselling. We tested a polygenic risk score (PRS) for AAD (PRS14AAD) as a tool to reevaluate disease etiology and identify patients misdiagnosed with AAD.
Methods:
We calculated the PRS14AAD in a cohort of patients diagnosed with AAD but lacking 21-hydroxylase autoantibodies (n=124), the main diagnostic marker of the disease. Patients with low genetic susceptibility to AAD were selected for whole-genome sequencing to detect potential monogenic causes (n=35).
Results:
Among the 35 patients, monogenic PAI was diagnosed in 5 (14%) and suspected in 3 additional cases (9%). Three out of the 5 patients diagnosed with monogenic PAI developed the disease in adulthood, indicating late-onset monogenic disease associated with hypomorphic genetic variants.
Conclusion:
A PRS for AAD can help identify potential monogenic cases, regardless of the age at diagnosis. Early identification of the underlying cause of PAI enables accurate management and correct genetic counselling.

141: From multi-omics to better health – Managing the biological data resource in the Norwegian Mother, Father and Child Cohort Study (MoBa)

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Longitudinal open-ended cohort studies, such as the Mother Father and Child study (MoBa), represent a unique research infrastructure with a rich array of various data types and biological materials. The aim of MoBa is to identify causality and etiology of disease in the population, with a particular focus on pregnancy and early lifespan. This knowledge can be used to prevent adverse health outcomes, optimize and personalize health care, and allow for new drug discoveries. MoBa is a nationwide study with a total of 285,000 participants, with the parent generation recruited between 1999 and 2008. Biological samples have been collected from the full cohort, and several MoBa sub-studies continue to enrich the biobank. Today, the millions of aliquots stored in the biobank at FHI offer full-blood, plasma, DNA, and urine for researchers to analyze. Despite the large number of samples in total, it is a limited resource on the level of each individual participant. Optimal use of the biobank samples should thus facilitate the use of several technologies (multi-omics) that enable the capture of biological information flow (central dogma) and the effect of environmental exposures. FAIR documentation, standardization and harmonization of large-scale molecular datasets allows researchers to reuse data for new types of analyses, which may include data from other cohorts and registries. In contrast to the biological samples, these datasets may in theory be used by an indefinite number of projects. The biological data resource in MoBa now approximately includes whole-genome SNP-array data on 235,000 participants, methylation array data on 15,000 participants, and metabolomics data on 15,000 participants, with steadily increasing overlap on data from each participant, all thanks to individual research projects. The nature of large-scale molecular data demands tailored infrastructures and scientific-oriented management models, including bioinformatic pipelines to ensure data quality, increased availability, and ease of use.

142: The role of biobank in monitoring the immune system of hemato-oncological patients undergoing modern immunotherapy

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Poster session, Cosmos 3CD, september 11, 2024, 12.00 - 14.00

Background
The Biobank at University Hospital Ostrava focuses on archiving biological samples from patients with hematological malignancies with a special emphasis on monoclonal gammopathies. Currently, the Biobank is involved in one of the leading topics, immunomonitoring, which includes creating a cohort of samples from patients treated with modern immunotherapies to enhance understanding of immune responses and improve therapeutic strategies.
Aims
This research project aims to explore changes in immune cells and cytokine profiles induced by modern immunotherapies, such as T cell redirected therapy with T cell engagers (TCEs) and CAR T cell therapy. By integrating immune and genomic changes, the project seeks to identify biomarkers for predicting treatment outcomes and therapy-related toxicities.
Methods
Patients receiving the selected therapy were enrolled in the project after signing the informed consent form. The cohort consisted of patients newly diagnosed with or relapsed/refractory to multiple myeloma (MM), B-cell non-Hodgkin lymphoma (B-NHL), and chronic lymphocytic leukemia (CLL). Patients were divided into three cohorts: 1) anti-BCMA CAR T cell therapy; 2) T cell engagers (TCEs): a) anti-BCMA/CD3 (teclistamab, elranatamab), b) anti-GPRC5D/CD3 (talquetamab), c) anti-FcRH5/CD3 (cevostamab); 3) control cohort: a) daratumumab-based regimen, b) isatuximab-based regimen. As part of immunomonitoring, peripheral blood (PB) samples were collected at carefully chosen time points: before treatment (CAR T cell: before lymphodepletion; TCE: day 1), and subsequently on days 7, 14, 21, and months 1, 2, 3, 6, 9, 12, 24, and/or at the time of progression. The collected peripheral blood (1x EDTA, 1x Serum Gel) was centrifuged to obtain serum and plasma, which were then archived and stored at -80°C. Cryopreserved plasma samples were subsequently analyzed using a multiplex assay to determine the profiles of 48 cytokines. Bone marrow (BM) biopsy samples were obtained before treatment and at the time of progression; mononuclear cells were isolated (BMMC) and cryopreserved for future genomic and transcriptomic analyses.
Results:
A total of 62 patients participated in the study (Table 1), comprising 43 with multiple myeloma (MM), 18 with B-cell non-Hodgkin lymphoma (B-NHL), and 1 with chronic lymphocytic leukemia (CLL). In total, 450 peripheral blood collections were performed, resulting in the archiving of 4,950 aliquots. Cryopreserved plasma samples from 7 patients (teclistamab: n=3, talquetamab: n=3, cilta-cel: n=2) were analyzed using a multiplex assay to profile 48 cytokines at 10 time points during the first year of treatment. This analysis revealed significant cytokine profile variations among treatment subgroups. While the sample size is too small for definitive conclusions, preliminary data suggest that cytokine profiling could help identify potential biomarkers. Additionally, a spectral flow cytometry panel was developed to assess over 20 immune cell subpopulations before, during, and after CAR T and TCE therapies. The archived PB and BM samples will facilitate additional analyses within this project.
Conclusion
The Biobank has played a crucial role in organizing this project, primarily by ensuring that the selected time points have been maintained. Data from samples analyzed up to this point, along with archived samples, continue to provide a critical basis for future research projects and grant applications.